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[Intervention Review]

Fibrin sealant use for minimising peri-operative allogeneic blood transfusion

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ABSTRACT

Background

Fibrin sealants (also referred to as biological glue or fibrin tissue adhesives) have gained increasing popularity as interventions to improve peri-operative (intra- and post-operative) haemostasis and diminish the need for allogeneic red cell transfusion (blood from an unrelated donor).

Objectives

To examine the efficacy of fibrin sealants in reducing peri-operative blood loss and allogeneic red blood cell (RBC) transfusion.

Search methods

We identified studies by searching CENTRAL (*The Cochrane Library* 2007, Issue 3), MEDLINE (1950 to 2008), EMBASE (1980 to 2008), manufacturer web sites (to March 2008), and bibliographies of relevant published articles.

Selection criteria

Controlled trials in which adult patients scheduled for elective surgery were randomised to fibrin sealant treatment or to a control group which did not receive fibrin sealant treatment. Trials were eligible if they reported data on the number of patients exposed to allogeneic red cell transfusion, the volume of blood transfused, or blood loss (assessed objectively).

Data collection and analysis

The primary outcomes measured were the: number of patients exposed to allogeneic red cells, amount of blood transfused, and blood loss. Other outcomes measured were: re-operation due to bleeding, infection, mortality, thrombotic events, and length of hospital stay. Treatment effects were pooled using a random-effects model.

Main results

Eighteen trials that included a total of 1406 patients reported data on peri-operative exposure to allogeneic RBC transfusion. Fibrin sealant treatment, on average, reduced the rate of exposure to allogeneic RBC transfusion by a relative 37% (relative risk (RR) 0.63, 95% confidence interval (CI) 0.45 to 0.88) and 7% in absolute terms (95% CI 2% to 13%). Fourteen trials, including a total of 853 patients, provided data for post-operative blood loss. In aggregate, fibrin sealant treatment reduced blood loss on average by around 161 ml per patient (95% CI 98.25 to 224.53 ml). In the context of orthopaedic surgery, fibrin sealant treatment reduced post-operative blood loss on average by around 223 ml per patient (95% CI 119.85 to 325.18 ml) and reduced the risk of exposure to allogeneic RBC transfusion by 32% (RR 0.68, 95% CI 0.51

to 0.89). Fibrin sealant treatment was not associated with an increased risk of wound infection (RR 0.61, 95% CI 0.24 to 1.58), any infection (RR 0.93, 95% CI 0.44 to 1.94), haematoma formation (RR 0.46, 95% CI 0.18 to 1.18), or death (RR 0.85, 95% CI 0.38 to 1.89). Hospital length of stay was not reduced in patients treated with fibrin sealant (weighted mean difference (WMD) -0.21 days, 95% CI -0.42 to 0.01 days).

Authors' conclusions

Overall, the results suggest that fibrin sealants are efficacious in reducing both post-operative blood loss and peri-operative exposure to allogeneic RBC transfusion. Although treatment-effect heterogeneity was observed for these primary efficacy outcomes, heterogeneity was generally in terms of the size of effect rather than the direction of effect. Fibrin sealants appeared to demonstrate their greatest beneficial effects in the context of orthopaedic surgery, where blood loss is often substantial. Trials not involving orthopaedic surgery generally showed a trend toward decreased post-operative blood loss but the observed reductions were not clinically significant. The majority of trials included in this review were small, which raises concerns about the potential effects of publication bias. Funnel plot assessment indicates that there is some evidence of publication bias in the form of a missing population of small negative trials. We believe that large, methodologically rigorous, randomised controlled trials of fibrin sealants are needed.

PLAIN LANGUAGE SUMMARY

Fibrin sealants have fewer proven benefits than some other technologies designed to reduce the risks associated with transfusions of donated blood

Fibrin sealants are composed of specific blood clotting agents that, when applied to wound surfaces, help stop bleeding. In liquid form, fibrin sealants are generally sprayed directly onto wound surfaces. They are often used to try to reduce blood loss during and after surgery and therefore avoid blood transfusions. Although fibrin sealant components are derived from blood products, they have a lower risk of transmitting infections than donor blood. The review of trials found that fibrin sealants can reduce surgical blood loss and the need for blood transfusion. Fibrin sealants appear to be most effective when used in orthopaedic surgery.

BACKGROUND

Description of the intervention

Red blood cell transfusions are an extremely common medical intervention. Of all red blood cell units transfused, between 60% and 70% are used in the surgical setting (Hasley 1995; Hebert 1997). Worldwide concern regarding the safety of transfused blood has prompted a reconsideration of the role of allogeneic blood transfusion (whole blood or packed red cells from an unrelated donor). Although allogeneic blood transfusion has had a unique place in medical practice, the evidence on the benefits, harms, and costs of a range of techniques designed to minimise the use of this scarce resource needs to be critically examined. Some of the alternatives to allogeneic blood transfusion have their own risks and are expensive (Coyle 1999; Fergusson 1999a).

The International Study of Peri-operative Transfusion (ISPOT) (a 10-country study of evidence, attitudes, and practices relating to the use of alternatives to peri-operative allogeneic blood transfusion) generated a number of systematic reviews that examined the efficacy and safety of various technologies employed to minimise the need for peri-operative allogeneic blood transfusion (Bryson 1998; Forgie 1998; Huet 1999; Laupacis 1997; Laupacis 1998). Amongst the various technologies studied were the anti-fibrinolytic drugs, aprotinin, tranexamic acid, and epsilon aminocaproic acid; desmopressin (deamino-8-D-arginine vasopressin or DDAVP); autologous blood donation by pre-operative deposit (PAD); acute normovolaemic haemodilution (ANH); and cell salvage (CS). Findings from these studies indicate that PAD, ANH, and CS (techniques for re-infusing a patient's own blood and not for reducing blood loss) are associated with relatively small benefits in terms of reducing the need for allogeneic blood. However, the use of those technologies intended to reduce surgical blood loss, such as with aprotinin and tranexamic acid, are associated with significant benefits in terms of reducing the need for allogeneic blood transfusion (Henry 2007).

Fibrin sealants are a technology intended to reduce surgical blood loss. They have been used in surgery for more than 20 years (Martinowitz 1996a) and many surgeons have advocated that they are the material that best approaches the ideal operative sealant (Gibble 1990). Recognition of their potential as haemostatic agents has seen their use expand across a range of surgical settings, including cardiovascular, orthopaedic, thoracic, and orthodontic surgery (Sierra 1993).

As a biological agent, fibrin has been used since the turn of the 20th century. As early as 1909, Bergel (Bergel 1909) reported the use of dried plasma as a source of fibrinogen and fibrin fleece to establish surgical haemostasis. The first use of plasma fibrinogen mixed with bovine thrombin was reported in 1944 (Cronkite 1944). The mixing of bovine thrombin with physiological fibrinogen (2 to 5 mg/ml) as a means of accelerating the formation of the fibrin clot was also reported by Tidrick and Warner (Tidrick 1944). After these early studies enthusiasm for fibrin sealants subsided, due in part to the suboptimal adhesive properties and inadequate strength of the sealants used (Matras 1985). The lack of a concentrated source of fibrinogen was cited by Matras (Matras 1985) as the reason for the suboptimal adhesive properties of the early sealants. Early studies were also mainly limited to the direct application of dry fibrin or fibrin tampons to bleeding surfaces (Radosevich 1997).

With improvements in plasma fractionation methods and the availability of concentrated fibrinogen, significant progress was made in improving the rheological properties (elasticity, tensile strength, adhesiveness) of fibrin sealants (Radosevich 1997). During the late 1970s the first commercial, multi-donor, fibrin sealant products were made available throughout Europe (Gibble 1990). However, as the first commercial fibrin sealants relied on a consistent and concentrated source of human fibrinogen, the Food and Drug Administration in the United States revoked the licence for the clinical use of pooled commercial fibrinogen concentrates due to the high risk of hepatitis transmission with the fibrinogen (Gibble 1990).

In an attempt to resolve this issue, most commercial products adopted various viral inactivation procedures including pasteurisation (60 °C for 10 hours, liquid state), solvent-detergent treatment, steam treatment (60 °C for 30 hours, dry state), ultraviolet C (UVC) irradiation, nanofiltration (35 nm), and dry heat treatment (100 °C for 30 minutes). Although some of these procedures are effective against lipid-enveloped viruses, not all inactivate non-enveloped viruses present in human plasma, such as parvovirus B19 and hepatitis A virus (HAV). UVC irradiation in the presence of rutin (a free radical scavenger added to protect plasma protein biological activity) has been shown to be effective against such viruses (Radosevich 1997). Experimental studies in mice have shown nanofiltration (using a 35 nm pore size filter membrane) to be effective in removing the Creutzfeld-Jakob agent from infected brain extracts and, therefore, this technique may be of benefit in reducing the risks of prion disease transmission via fibrin sealants in humans (Tateishi 1993).

Although the risks of viral transmission from fibrin sealants prepared from pooled human plasma are considered to be low, there has been a concerted effort to develop fibrin sealant systems that utilise autologous fibrinogen as opposed to fibrinogen obtained from single or random donor pooled plasma. However, a 'zero' risk cannot be guaranteed, even with the use of autologous fibrinogen, as microbial and viral contamination from operators, equipment, or both, may occur during the processing phase (Radosevich 1997).

Currently, a number of commercial and 'home-made' (blood bank prepared) sealants are used throughout the world. Although the composition of the components and the methods of preparation vary considerably in each of the commercial and 'home-made' products their primary components remain similar.

Fibrin sealants generally contain two major components. These are fibrinogen (with or without factor XIII) and thrombin (plus calcium, usually in the form of calcium chloride). Fibrinogen, the main structural component in fibrin sealants, is a protein produced primarily by liver hepatocytes and secondarily by platelets that circulates in plasma at a concentration of 2 to 5 mg/ml. Thrombin is a serine protease that is generated from an inactive form (prothrombin) by the enzyme prothrombinase in the presence of calcium (Sierra 1993). During the final phase of the coagulation cascade, thrombin in the presence of calcium converts fibrinogen to insoluble, loose fibrin threads. Fibrin sealants facilitate haemostasis by mimicking this final phase of the coagulation cascade which leads to the formation of a semi-rigid clot (Radosevich 1997). The components of fibrin sealants are commonly applied to the wound surface simultaneously using single- or dual-syringe systems that deliver the sealant in a liquid

or aerosolised form. The dual-syringe system is designed in such a way that the sealant components are mixed passively while exiting the syringe, just prior to wound contact. To provide a fine, more uniform film of sealant on the wound surface, spray devices that aerosolise the sealant using small, portable gas propellant systems are frequently used. Whereas liquid application using fine needle delivery systems is more suitable for small wound surfaces, fibrin sealants delivered using spray devices are more appropriate for diffuse, slow bleeding and large body surfaces (Radosevich 1997).

Why it is important to do this review

Reviews of fibrin sealants are abundant, however the majority are narrative reviews that primarily provide information regarding scientific or technical aspects of fibrin sealants (Dunn 1999; Gibble 1990; Green 1996; Jackson 1996; Kjaergard 1996; Martinowitz 1996a; Martinowitz 1996b; McCarthy 1993; Radosevich 1997; Sierra 1993). This review builds on the systematic review originally published by the author (Carless 2002) and examines the evidence on the efficacy of fibrin sealants in reducing peri-operative blood loss and allogeneic RBC transfusion in adult, elective surgery.

OBJECTIVES

To examine the efficacy of fibrin sealants in reducing peri-operative (intra- and post-operative) blood loss, allogeneic red blood cell (RBC) transfusion, and the evidence for any effect on clinical outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) with a concurrent control group.

We only considered trials that reported data on the number of patients exposed to allogeneic red blood cells, amount of blood transfused, or blood loss to be eligible for review. We only included those trials that assessed blood loss objectively (for example blood loss expressed in millilitres). We did not consider for review trials that provided subjective assessment of blood loss (for example blood loss measured on an interval rating scale). We included studies if they were published in English, German, French, or Italian (based on the availability of translators). We excluded duplicate publications.

Types of participants

The study participants were adults (over 18 years). The surgery performed was elective or non-urgent. We did not consider trials involving emergency procedures.

Types of interventions

The intervention considered was fibrin sealant. We only considered those studies that investigated the use of fibrin sealants applied to the wound surface in either liquid or aerosolised form. We did not consider trials that studied bandages or pads impregnated with lyophilised fibrin sealant components.

Types of outcome measures

Primary outcomes

1. Number of patients exposed to allogeneic red cell transfusion
2. Volume of blood transfused (expressed as units of blood)
3. Blood loss (expressed in millilitres)

Secondary outcomes

1. Frequency of re-operation for bleeding
2. Any infection
3. Wound infection
4. Haematoma formation
5. Stroke
6. Wound dehiscence
7. Mortality
8. Length of hospital stay

Search methods for identification of studies

The searches were not restricted by language or publication status.

Electronic searches

Searches were conducted by the authors, working independently from the Cochrane Injuries Group Editorial base.

The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE, and EMBASE databases were initially searched using unrestricted search strategies, with exploded MeSH (medical subject heading) terms and specific text-word terms for fibrin sealant. The exploded MeSH terms included: 'fibrin tissue adhesive' and 'fibrin glue'. The specific text-word terms included: fibrin glue$, fibrin sealant$, fibrin seal$, biological glue$ or biological seal$, beriplast, bolheal, tissucol, tisseel, quixil, biocol, cryoseal.

To restrict and improve the specificity of these searches, two search filters were used. Firstly, a filter developed by the ISPOT (International Study of Peri-operative Transfusion) group (Laupacis 1997) which identifies blood transfusion trials using the MeSH terms: 'blood transfusion', 'hemorrhage', and 'anesthesia'; the ISPOT filter combines these MeSH terms with the text-word terms: transfusion$, bleed$, blood loss$, hemorrhag$. Secondly, an RCT filter (Dickersin 1994; Robinson 2002) was used to identify randomised controlled trials.

These search filters were combined with the specified MeSH terms and the relevant text-word terms for fibrin sealant.

We searched the following electronic databases:

- CENTRAL (*The Cochrane Library* Issue 3, 2007);
- MEDLINE (1950 to March 2008);
- EMBASE (1980 to March 2008).

The detailed search strategies are recorded in Appendix 1.

Searching other resources

We searched the bibliographies of eligible trials, review articles, and reports for further potentially relevant studies.

In addition to the computer database searches, we searched manufacturer's Internet sites and contacted experts in the field to identify reports or projects in progress relevant to this review.

Data collection and analysis

Selection of studies

One author (PAC) screened titles and abstracts of identified studies and selected trials that met the defined eligibility criteria. We used an article extraction form to extract information regarding randomisation criteria, study methodology, the presence of a transfusion protocol, type of surgery, treatment outcomes, and general comments. Two independent raters (PAC, DMA) examined articles for inclusion and exclusion criteria, with disagreements resolved by consensus.

Data extraction and management

We extracted data from studies using a data extraction form and entered the data into Review Manager 5 (RevMan 5). We recorded data on the following outcomes: the number of patients exposed to allogeneic red cell transfusion, volume of blood transfused (expressed as units of blood), blood loss (expressed in millilitres), re-operation for bleeding, any infection, wound infection, haematoma formation, stroke, wound dehiscence, thrombosis, mortality, and length of hospital stay. We also recorded information regarding demographics (age, sex), the type of surgery, and the presence or absence of a transfusion protocol. We extracted data for allogeneic transfusion if these were expressed as whole blood or packed red cells. We also extracted data regarding the type of fibrin sealant used and the method of application. We documented the number of patients who were enrolled, randomised, and completed the study.

Assessment of risk of bias in included studies

Articles were assessed for methodologic quality by two of the authors (PAC, DMA) using criteria proposed by Schulz et al (Schulz 1995). These criteria involve four items of assessment: double-blinding, allocation concealment, participant exclusion (withdrawal post-randomisation), and the methods used to achieve randomisation. In the case of double-blinding, allocation concealment, and participant exclusion, three numeric values (0, 1, 2) were allocated to each of the three scales within each of these items. For example, trials judged to have adequately concealed treatment allocation scored 2, whereas trials judged not to have concealed treatment allocation scored 0. In the case of the method used to achieve randomisation, two numeric values (0, 1) were allocated to each of the two scales within this item of assessment. Therefore, trials scored 1 if the method used to generate allocation sequences was judged to have been adequate (for example random number table, computer random number generator), whereas inadequate or unreported methods scored 0.

Inter-rater agreement for each item of methodological quality assessment was assessed by comparing the observed or achieved agreement (the proportion of studies for which the two raters assigned the same score) with that expected by chance (the agreement that would be achieved if the raters assigned scores at random). STATA® statistical software was used to calculate agreement and kappa statistics (κ). Disagreements were resolved by consensus.

The methodological quality of included trials was also assessed with particular emphasis on allocation concealment, which was ranked as follows.

- Grade A - adequate concealment.
- Grade B - uncertain.
- Grade C - inadequate allocation concealment.

Data synthesis

We analysed dichotomous data (for example number of patients transfused, infection, thrombosis, patients requiring re-operation for bleeding) and continuous data (for example mean units of blood transfused, and mean volume of blood loss) using Review Manager 5 (RevMan 5). If standard deviations (SD) or standard error of means (SEM) were not reported for continuous data (or could not be calculated from raw data or summary estimates) we did not include the study in the meta-analysis. We expressed dichotomous outcomes as pooled relative risks (RR) or risk differences (RD) and weighted mean differences (WMD) for continuous variables using a random-effects model. We used the Q statistic to assess heterogeneity of treatment effect, which has an approximate Chi^2 distribution with degrees of freedom equal to the number of studies minus one (Der Simonian 1986). We used a P value less than or equal to 0.1 to define statistically significant heterogeneity. The I^2 statistic was used to quantify inconsistency across trials. The I^2 statistic describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (Higgins 2002; Higgins 2003).

Subgroup analysis and investigation of heterogeneity

We performed analysis of a priori subgroups to determine whether effect sizes varied according to factors such as the type of surgery, the use of transfusion protocols, and the type of fibrin sealant. Funnel plots were inspected for evidence of publication bias.

RESULTS

Description of studies

Results of the search

We identified 28 randomised controlled trials of fibrin sealant that involved elective surgery in adult patients and reported information for the main outcomes of interest. Of these, 26 fulfilled the inclusion criteria. The two trials that were excluded (Courtade 1996; Shiono 1998) used actively treated (fibrin sealant) control groups.

Included studies

Of the 26 included trials, 77% (n = 20) recruited less than 50 patients in each arm. The trials were conducted in a range of countries: United States (n = 6), Germany (n = 3), Denmark (n = 3), Japan (n = 3), France (n = 2), United Kingdom (n = 2), Spain (n = 2), Taiwan (Republic of China) (n = 1), Sweden (n = 1), India (n = 1), Ireland (n = 1), and Israel (n = 1). The majority of trials were published in English (88.5%). Two trials (Gasser 1983; Vecsey 1980) were published in German and one was published in French (Wurtz 1991). These studies were translated before being included in the analysis.

The trials were heterogeneous in terms of surgical setting and nature of the intervention (type of fibrin sealant and method of application). Trials were conducted across a range of surgical

settings including orthopaedic surgery (n = 7), liver surgery (n = 5), vascular surgery (n = 4), prostate surgery (n = 3), thoracic surgery (n = 3), renal surgery (n = 1), pancreatic surgery (n = 1), cardiac surgery (n = 1), and plastic surgery (incisional hernia repair with dermolipectomy) (n = 1).

There was also considerable variation in the type of fibrin sealant studied. Five trials investigated Tissucol®/Tisseel® (Immuno AG, Vienna, Austria), three studied Beriplast® P (Beringwerke/ Centeon, Marburg, Germany; FSBP, Aventis Behring, Strasbourg, France), five studied Omrixil®/Quixil® (Omrix Biopharmaceuticals SA, Israel and Belgium; Johnson & Johnson Wound Management, Somerville, New Jersey), two studied Biocol® (LFB, Les Ulis, France), three investigated an autologous fibrin sealant produced by the Vivostat® system (Conva Tec, Bristol-Meyers Squibb; Vivolution A/S, Denmark), two trials studied Hemaseel APR (Hemacure Corporation, Sarasota, FL, USA; Baxter Health Care Corporation, CA, USA), one studied a fibrin sealant produced by the Scottish National Blood Transfusion Service (SNBTS) and the Central Regional de Transfusion Sanguine (CRTS, Lille, France), one trial investigated an autologous fibrin sealant produced by the CryoSeal® FS system (ThermoGenesis Corporation, CA, USA), one trial studied a fibrin sealant produced by the Baxter Healthcare Group (Hyland Division, USA) and the American Red Cross, and one trial studied an autologous fibrin sealant.

The trials conducted by Vecsey (Vecsey 1980) and Gasser et al (Gasser 1983) used fibrin sealant components obtained from various manufacturers. The cryoprecipitate-fibrinogen was obtained from Immuno AG, Wien, and the thrombin solution (Topostatin®) was obtained from Hoffman-La Roche, Basel. Both these trials used collagen fleece as a carrier for the fibrin sealant. The trial conducted by Gasser et al (Gasser 1983) used collagen fleece obtained from Disperga, Wien, and the trial conducted by Vecsey (Vecsey 1980) used collagen fleece obtained from Pentapharm AG, Basel. These two trials used 150 cm^2 of collagen fleece to contain the fibrin sealant. The factor XIII concentrate used by Gasser et al (Gasser 1983) was obtained from Behringwerke, Hamburg. Both trials used the anti-fibrinolytic agents aprotinin (Trasylol®) and epsilon aminocaproic acid (Episkapron®) as clot stabilising agents.

Each of the different types of fibrin sealant studied varied in composition. The fibrinogen content ranged from 29 to 115 mg/ml, whereas the thrombin concentration ranged from 200 to 1000 IU/ml (international units per millilitre). In the case of the fibrin sealant produced by the CryoSeal® FS system, studies by Buchta et al and Rock et al (Buchta 2004; Rock 2003) indicated that the fibrinogen content of this product is around 22 ± 7 mg/ml and the thrombin content is around 38 to 46 U/ml. The autologous fibrin glue used by Mawatari et al (Mawatari 2006) contained around 249 ± 23 mg/ml of fibrinogen. In this study the auto-Cryo containing fibrinogen and other coagulation factors (Solution A) was mixed intra-operatively with Solution B which contained thrombin (5000 IU), 5 ml of 2% calcium chloride, and aprotinin (50,000 IU). The use of anti-fibrinolytic agents also varied with the different agents studied. The aprotinin content ranged from 1000 to 10,000 KIU/ml (kallikrein inhibitor units per millilitre). The fibrin sealant Quixil™ contained 95 mg/ml of tranexamic acid (TXA) as the anti-fibrinolytic agent. Where studies failed to provide product details we contacted authors and used manufacturer web sites to source information pertaining to the fibrin sealant components.

Risk of bias in included studies

Two raters assessed 22 of the 26 included trials for methodological quality. Four trials were excluded from the analysis of the reliability of quality assessment procedure because they were either an abstract (Stutz 2004) or were foreign language publications requiring translation by a single rater (Gasser 1983; Vecsey 1980; Wurtz 1991).

The inter-rater agreement for the assessment of methodological quality was good. For all four items of the Schulz criteria used to assess trial quality, the observed agreement was statistically, significantly better than chance (as indicated by a kappa value being statistically significantly different from zero). Kappa scores ranged from 0.84 to 1.0, being lowest in the case of the items measuring allocation concealment (κ = 0.84) and blinding (κ = 0.86).

Allocation

Allocation concealment

For the item of the Schulz criteria pertaining to allocation concealment the consensus scores were (out of a maximum score of 2): 2 for one trial, 1 for 10 trials, and 0 for 11 trials. There was 91% agreement (κ = 0.84) between the two raters for this item of assessment. Using the Cochrane criterion for grading allocation concealment, one trial was classified as Grade A (adequate allocation concealment) and 10 trials were classified as Grade C (inadequate allocation concealment). For the remaining 11 trials the method used to conceal treatment allocation was unclear and therefore we classified them as Grade B.

Inclusion of all randomised participants

Seventeen trials either reported that there were no exclusions or used intention-to-treat analysis. In three trials, where exclusions were reported, these exclusions were judged unlikely to cause bias. For the remaining two trials exclusions were not reported although there appeared to be some loss to follow up. There was 100% agreement between the two raters for this item.

Generation of allocation sequences (randomisation)

Trials assessed as having an adequate method of randomisation used either random number tables or computer-generated random numbers. For the item of the Schulz criterion pertaining to the generation of allocation sequence, the consensus scores were (out of a maximum score of 1): 1 for seven trials and 0 for 15 trials. There was 100% agreement between the two raters for this item.

Blinding

Blinding of outcome assessment was either not described or not reported for 18 of the 22 trials (82%) assessed for methodological quality.

Other potential sources of bias

Summary of trial methodological quality

The aggregate quality scores (maximum score of 7) were particularly low, with the majority of trials (82%) scoring less than or equal to 3 out of 7. This indicates that the overall methodological quality of the 22 assessed trials was poor. In summary, full blinding of outcomes assessment did not occur in any study, although partial blinding (single-blinding) was reported in one trial (Kjaergard 1998). In three trials, patients were either

blind to treatment assignment or the outcomes were assessed by an individual blind to the allocated patient treatment schedule (Belboul 2004; Fabian 2003; Molloy 2007).

The majority of trials (68%) failed to report the method used to generate allocation sequences (the randomisation process). Of the seven trials that described the method used to generate the allocation sequence, one reported using central randomisation (Levy 1999), four reported using computer-generated random sequences (Belboul 2004; Lassen 2006; Lillemoe 2004; Mawatari 2006), and two reported using randomisation codes placed in sealed envelopes (Jackson 1999; Kohno 1992). The latter method has the potential to be unmasked, leading to the potential for selection bias in the inclusion of patients to the trials (Schulz 1995). Follow up appears to have been complete in all but five trials (Kjaergard 1998; Lassen 2006; Noun 1996; Shah 2006; Wang 2001) which reported a small number of exclusions, so differential withdrawal is an unlikely source of bias.

Figure 1 and Figure 2 give a visual representation of the risk of bias for each included study. The risk of bias figures indicate that the general methodological quality of the trials was poor. Although all of the trials included in this review were described as being randomised, the majority of trials failed to report the method used to generate the allocation sequence. There was a similar lack of reporting of the methods used to conceal treatment allocation.

Figure 1. Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.

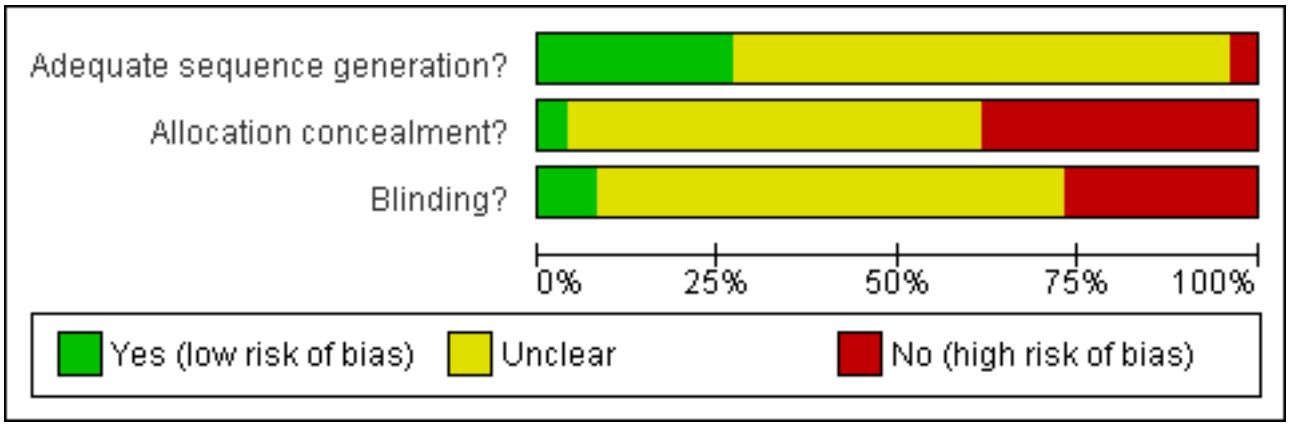


Figure 2. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.

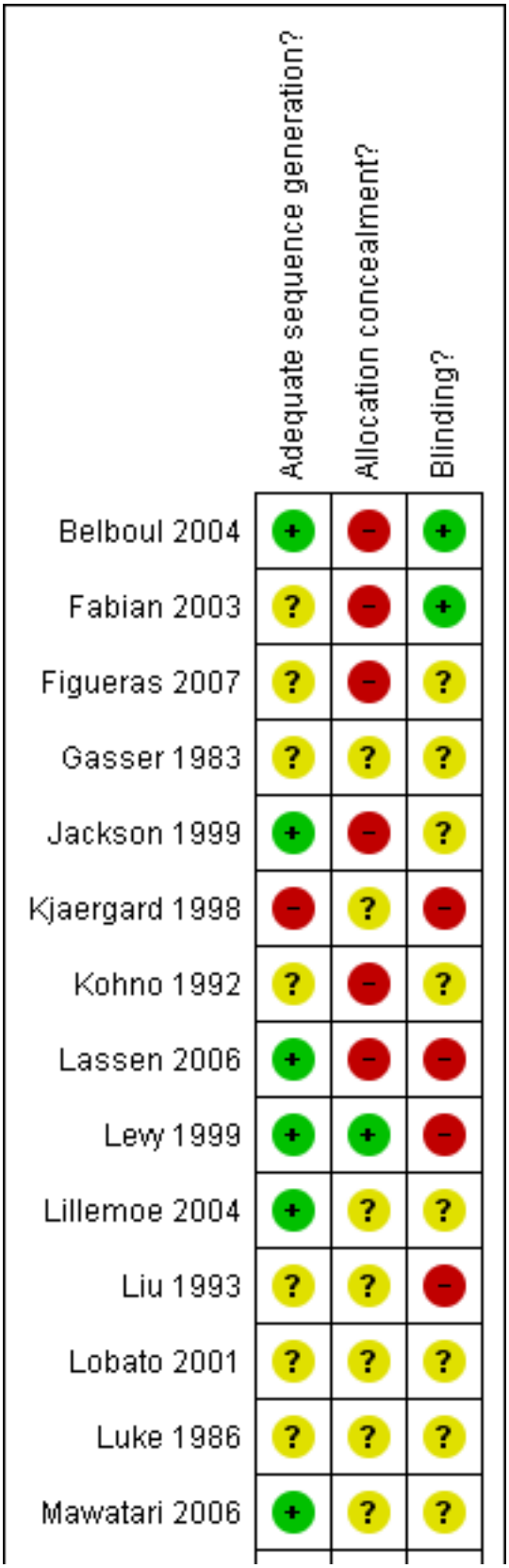
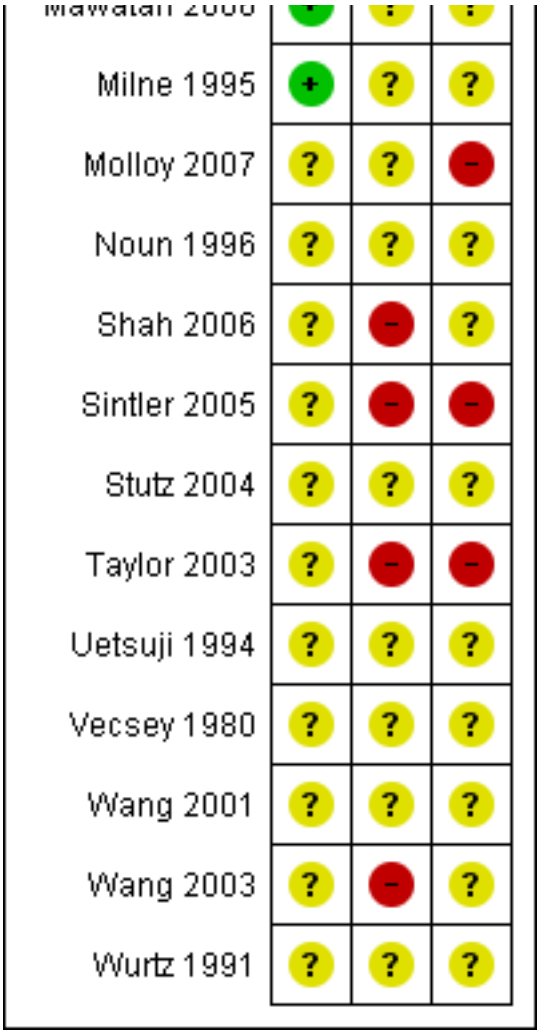


Figure 2. (Continued)



Effects of interventions

Exposure to allogeneic blood transfusion

Eighteen trials of fibrin sealant reported data for the number of patients exposed to allogeneic red cell transfusion. These trials included a total of 1406 patients of whom 698 were randomised to fibrin sealant. Overall, the use of fibrin sealant significantly reduced the rate of allogeneic blood transfusion by a relative 37% (RR 0.63, 95% CI 0.45 to 0.88) compared to control. Heterogeneity between these trials was statistically significant (P = 0.03; I^2 = 45%). The absolute risk reduction (ARR) was 7% (RD -0.07, 95% CI -0.13 to -0.02).

Exposure to allogeneic blood transfusion - type of surgery

With the exception of orthopaedic trials, this subgroup analysis was constrained by the small number trials in each strata. Generally fibrin sealant treatment appeared to be most beneficial when used in prostate surgery (RR 0.32, 95% CI 0.17 to 0.61). However, it should be noted that one trial (Gasser 1983) within this subgroup provided 95.2% of the information (weight). In the case of orthopaedic surgery (n = 7 trials), the use of fibrin sealant significantly reduced the rate of allogeneic blood transfusion by a relative 32% (RR 0.68, 95% CI 0.51 to 0.89) compared to control (heterogeneity P = 0.45; I^2 = 0%).

Exposure to allogeneic blood transfusion - transfusion protocol

Of the 18 trials that reported data for the number of patients receiving an allogeneic red cell transfusion, four reported the use of transfusion protocols to guide transfusion practice. These four trials included a total of 481 patients of whom 240 were randomised to fibrin sealant treatment. For these trials the pooled relative risk of receiving an allogeneic red cell transfusion was 0.65 (95% CI 0.28 to 1.49) compared to an RR of 0.62 (95% CI 0.46 to 0.83) for those 14 trials that did not report the use of transfusion protocols.

Exposure to allogeneic blood transfusion - type of fibrin sealant

Subgroup analysis of the data in terms of the type of fibrin sealant was constrained by the small number of trials in each strata. There were five trials that investigated the fibrin sealant Quixil®. These trials included a total of 312 patients of whom 152 were randomised to fibrin sealant treatment. Four of these five trials involved orthopaedic surgery. The use of Quixil® significantly reduced the

rate of allogeneic red cell transfusion by a relative 41% (RR 0.59, 95% CI 0.41 to 0.84). The seven trials that investigated the fibrin sealant Tissucol®/Tisseel®/Hemaseel® involved various surgical procedures (thoracic, prostatic, liver, kidney, pancreatic) and included a total of 759 patients of whom 384 were randomised to fibrin sealant treatment. The use of Tissucol®/Tisseel®/Hemaseel® did not significantly reduce the risk of receiving an allogeneic red cell transfusion across a range of surgical settings (RR 0.53, 95% CI 0.19 to 1.50). A similar non-significant result was observed with the use of the Vivostat® system (RR 0.80, 95% CI 0.52 to 1.24).

Exposure to allogeneic blood transfusion - trial methodological quality

Only one trial was judged to have adequately concealed treatment allocation (Grade A). For this single trial the relative risk of receiving an allogeneic red cell transfusion was 0.31 (95% CI 0.13 to 0.74). There were 10 trials that failed to describe the method used to conceal treatment allocation (Grade B). For these trials the relative risk of receiving an allogeneic red cell transfusion was 0.52 (95% CI 0.37 to 0.74). In the case of the seven trials that were judged to have inadequately concealed treatment allocation (Grade C) the relative risk of receiving an allogeneic red cell transfusion was 0.93 (95% CI 0.63 to 1.36).

Volume of blood transfused

Eight trials reported data for the amount of blood transfused. These trials included a total of 685 patients of whom 332 were randomised to fibrin sealant treatment. Overall, the use of fibrin sealant reduced the amount of red blood cells transfused on average by around 0.27 units per patient (95% CI 0.01 to 0.54 units). Although this result is statistically significant, a reduction of less than half a unit of allogeneic RBC per patient does not translate into a clinically significant reduction.

Post-operative blood loss

Fourteen trials provided post-operative blood loss data. These trials included a total of 853 patients of whom 425 were randomised to fibrin sealant treatment. On average, fibrin sealant use statistically significantly reduced the volume of post-operative blood loss by around 161 ml per patient (95% CI 98 to 225 ml). Heterogeneity in treatment effect was statistically significant ($P < 0.00001$; $I^2 = 82\%$).

Post-operative blood loss - type of surgery

The greatest reductions in post-operative blood loss were observed in the seven trials that were conducted in the setting of orthopaedic surgery. These trials included a total of 482 patients of whom 235 were randomised to fibrin sealant treatment. When used in orthopaedic surgery, the use of fibrin sealant reduced blood loss by around 223 ml per patient (WMD -222.52 ml, 95% CI -325.18 to -119.85 ml). However, heterogeneity in treatment effect was statistically significant ($P < 0.0001$; $I^2 = 78\%$). For the two trials that were conducted in the setting of liver surgery, the use of fibrin sealant on average did not statistically significantly reduce the volume of post-operative blood loss (WMD -107.90 ml, 95% CI -370.68 to 154.88 ml). For the three trials that involved prostate surgery, the use of fibrin sealant was associated with a reduction in post-operative blood loss of around 70 ml per patient (WMD -70.25 ml, 95% CI -136.59 to -3.90 ml). Although this result is statistically significant, such small reductions in blood loss do not translate into clinically meaningful reductions. There were two trials that involved thoracic surgery. These trials included a total of 90 patients of whom 45 were randomised to fibrin sealant treatment. The use of fibrin sealant in this surgical context did not statistically significantly reduce the volume of post-operative blood loss (WMD -161.99 ml, 95% CI -586.20 to 262.21 ml).

Although the trial conducted by Kjaergard et al (Kjaergard 1998) reported that operative blood loss was lower in the group randomised to fibrin sealant (mean = 887 ml, median = 720 ml, range 420 to 1765 ml) than in the control group (mean = 1089 ml, median = 733 ml, range 200 to 3200 ml) the difference was not statistically significant ($P > 0.4$). The trial conducted by Sintler et al (Sintler 2005) reported a statistically significant reduction in blood loss in the fibrin sealant group compared to the control group following carotid clamp release. The median blood loss in the Quixil® fibrin sealant group was 24.5 ml (range 5.5 to 105.0 ml) compared to 203 ml (range 54.5 to 817.0 ml) in the Kaltostat® control group ($P < 0.001$). The trial conducted by Taylor et al (Taylor 2003) reported lower blood loss in the fibrin sealant group compared to the control group treated with thrombin soaked gauze (TSG) in patients undergoing polytetrafluoroethylene (PTFE) femoral artery grafts. In patients treated with Beriplast® fibrin sealant the median blood loss was 3.81 ml (± 28.27 ml) compared to 14.8 ml (± 27.03 ml) ($P < 0.0001$). In contrast, the trial conducted by Fabian et al (Fabian 2003) reported a mean blood loss of 440 ml in those patients treated with Hemaseel® fibrin sealant compared to 485 ml in those patients randomised to the control group ($P = 0.362$).

It should be noted that these trials were not included in the meta-analysis of blood loss due to the lack of usable data (means and SDs or SEMs were not reported).

Intra-operative blood loss

Seven trials including a total of 463 patients reported data for intra-operative blood loss. The use of fibrin sealant did not statistically significantly impact on intra-operative blood loss (WMD -4.51 ml, 95% CI -36.86 to 27.83 ml). For four of the seven trials, the fibrin sealant was not applied to the wound surface until at the end of the operative procedure, just prior to wound closure. As most of the intra-operative blood loss would have occurred prior to fibrin sealant application, the small difference in intra-operative blood loss between groups may well be expected. Any significant reductions in intra-operative blood loss may not necessarily reflect the efficacy of fibrin sealant treatment but rather reflect better surgical techniques or a greater propensity for some patients to achieve haemostasis in the face of physiological insult. The latter is greatly influenced by a patient's pre-operative exposure to antithrombotic or anticoagulant therapy, or both. In the case of the trial conducted by Lillemoe et al (Lillemoe 2004) greater blood loss was observed in fibrin sealant treated patients (800 ml) compared to the control group (650 ml).

Intra-operative blood loss - type of surgery

Of the seven trials that reported data for intra-operative blood loss three involved liver surgery. These trials included a total of 166 patients of whom 76 were randomised to fibrin sealant treatment. For these trials, fibrin sealant use did not statistically significantly reduce intra-operative blood loss (WMD -124.92 ml, 95% CI -545.32 to 295.49 ml). In the case of the three trials involving orthopaedic surgery, intra-operative blood loss was not statistically significantly reduced in those patients treated with fibrin sealant compared to

control (WMD -8.48 ml, 95% CI -45.79 to 28.84 ml). For the trial that involved vascular surgery (Jackson 1999), fibrin sealant use did not statistically significantly reduce intra-operative blood loss (P = 0.551).

Although the trial conducted by Milne et al (Milne 1995) reported that operative blood loss was lower in the group randomised to fibrin sealant (median = 420 ml, range 300 to 500 ml) than in the control group (median = 550 ml, range 350 to 1200 ml) the difference was not statistically significant. It should be noted that this trial was not included in the meta-analysis of blood loss due to the lack of usable data (means and SDs or SEMs were not reported).

Total blood loss - intra-operative and post-operative blood loss combined

Four trials reported data for total blood loss (intra- and post-operative). These trials included a total of 502 patients of whom 248 were randomised to fibrin sealant treatment. In aggregate, the use of fibrin sealant significantly reduced the amount of total blood loss compared to control (WMD -216.18 ml, 95% CI -406.26 to -26.10 ml). When data for the three orthopaedic trials were analysed separately, the amount of total blood loss was reduced on average by around 272 ml in those patients treated with fibrin sealant compared to control (WMD -271.99 ml, 95% CI 93.63 to 450.35 ml).

Mortality

Ten trials including a total of 1014 patients reported mortality data. Fibrin sealant use did not statistically significantly impact on the rates of mortality (RR 0.85, 95% CI 0.38 to 1.89). There were 11 reported deaths in fibrin sealant treated patients (11/501; 2.2%) compared to 13 deaths in control group patients (13/513; 2.5%). Four of these trials reported that no deaths occurred during the trial period. It should be noted that the majority of deaths (62.5%) occurred in just two trials, both involving liver surgery (Figueras 2007; Kohno 1992).

Re-operation for bleeding

Three trials provided information about re-operation for bleeding. These trials included a total of 340 patients of whom 169 were randomised to fibrin sealant treatment. Three patients in one trial (Figueras 2007) required a re-operation for bleeding; two of these patients were being treated with fibrin sealant.

Length of hospital stay

Five trials reported data for length of hospital stay. Fibrin sealant use was not associated with a reduced length of hospital stay (WMD -0.21 days, 95% CI -0.42 to 0.01 days; I^2 = 0%).

Adverse events and other outcomes

Fibrin sealant use did not statistically significantly impact on the rates of any infection (RR 0.93, 95% CI 0.44 to 1.94; I^2 = 0%), wound infection (RR 0.61, 95% CI 0.24 to 1.58; I^2 = 0%), haematoma formation (RR 0.46, 95% CI 0.18 to 1.18; I^2 = 0%), stroke (RR 0.37, 95% CI 0.02 to 7.99; I^2 = 0%), deep vein thrombosis (RR 3.0, 95% CI 0.13 to 71.92), or pulmonary embolus (RR 0.97, 95% CI 0.11 to 8.88; I^2 = 0%). However, the number of events for each of these outcomes was far too small to draw firm conclusions. No trials reported data for wound dehiscence (an a priori outcome).

DISCUSSION

The results indicate that fibrin sealant use resulted in an average reduction in post-operative blood loss of around 161 ml per patient. Further, the use of fibrin sealants reduced exposure to allogeneic red cell transfusion on average by a relative 37%; 7% in absolute terms. It is notable that for those trials that provided data for the number of patients transfused allogeneic red blood cells (RBC), there appeared to be very little correlation between blood loss and the rates of transfusion. Although patients treated with fibrin sealant were transfused far less frequently than controls (15.3% versus 21.8%), the differences in mean post-operative blood loss for these trials were quite small. The trial conducted by Levy et al (Levy 1999) was the only study where the reduction in mean post-operative blood loss was both clinically and statistically significant (mean difference = 705 ml, 95% CI 420.74 to 989.26 ml; P < 0.001). For this trial, 17% of the patients in the fibrin sealant group were exposed to allogeneic RBC compared to 55% in the control group. For the remaining trials the mean differences in post-operative blood loss ranged from just 23 ml to 358 ml, with blood transfusion exposure rates for the fibrin sealant groups ranging from 0% to 48.5% and the control groups ranging from 0% to 61%.

A number of factors may account for this apparent lack of correlation between blood loss and the frequency of blood transfusion. Firstly, blood loss may not have been measured or estimated accurately; blood extravasation (bleeding into surrounding tissues) cannot be evacuated by drainage systems and therefore cannot be measured directly (inapparent blood loss) although it can be estimated using various formulae (Gross 1983; Hahn 1989). Secondly, the decision to transfuse RBC was based on haemodynamic variables rather than blood loss. Thirdly, the decision to transfuse RBC was based on haematological variables (that is haemoglobin or haematocrit levels) or arbitrary transfusion thresholds rather than blood loss. Fourthly, in the absence of transfusion protocols, blood transfusion practice may have been somewhat haphazard. Fifthly, a disproportionate number of patients may have been donors and recipients of autologous blood; and finally, as the majority of studies were unblinded, knowledge of the patient's treatment schedule may have reversed a transfusion decision even when there was no clear clinical need.

It appears that in some cases the decision to transfuse may not have been based on clear clinical need, and the transfused volume may have been small. As the decision to transfuse (the primary outcome in this meta-analysis) is a practice variable rather than a clinical variable, it involves a degree of subjectivity. This raises questions about the validity of blood transfusion exposure as an outcome variable in unblinded trials. Blinding surgeons to the application of a topical haemostatic agent, where no suitable placebo is available, is difficult and therefore it is quite possible that those patients allocated to receive fibrin sealant treatment may have been transfused more conservatively during the peri-operative period. As only four trials (Figueras 2007; Kjaergard 1998; Levy 1999; Molloy 2007) provided details regarding the use of transfusion protocols, bias may have been introduced, potentially exaggerating the magnitude of beneficial effect of fibrin sealant treatment.

Adverse events

Despite the limited data, it appears that the potential benefit of fibrin sealants in reducing allogeneic red cell transfusion and post-

operative blood loss is not off-set by the serious adverse effects. However, it is important to note that the studies reviewed here, both individually and in aggregate, are not large enough to draw firm conclusions regarding adverse events.

Sources of bias

The majority of reviewed studies were small, with less than 60 participants in each arm. Reliance on small studies raises concerns about the effects of publication bias. Funnel plot assessment (Figure 3; Figure 4) indicates that there is some evidence of publication bias in the form of a 'missing population of small negative studies'. To model the effects of publication bias we generated a number of small negative 'unpublished' trials by reversing the results for the treatment and control groups in the small positive trials included in the review (Kjaergard 1998; Lobato 2001; Sintler 2005; Stutz 2004; Vecsey 1980). A meta-analysis of this augmented data set showed that the pooled relative risk of exposure to allogeneic blood transfusion was reduced from the original estimate of 0.63 (95% CI 0.45 to 0.88) to 0.72 (95% CI 0.51 to 1.03). Given this, the presence of publication bias cannot be discounted and as such the results may need to be viewed with some degree of caution.

Figure 3.

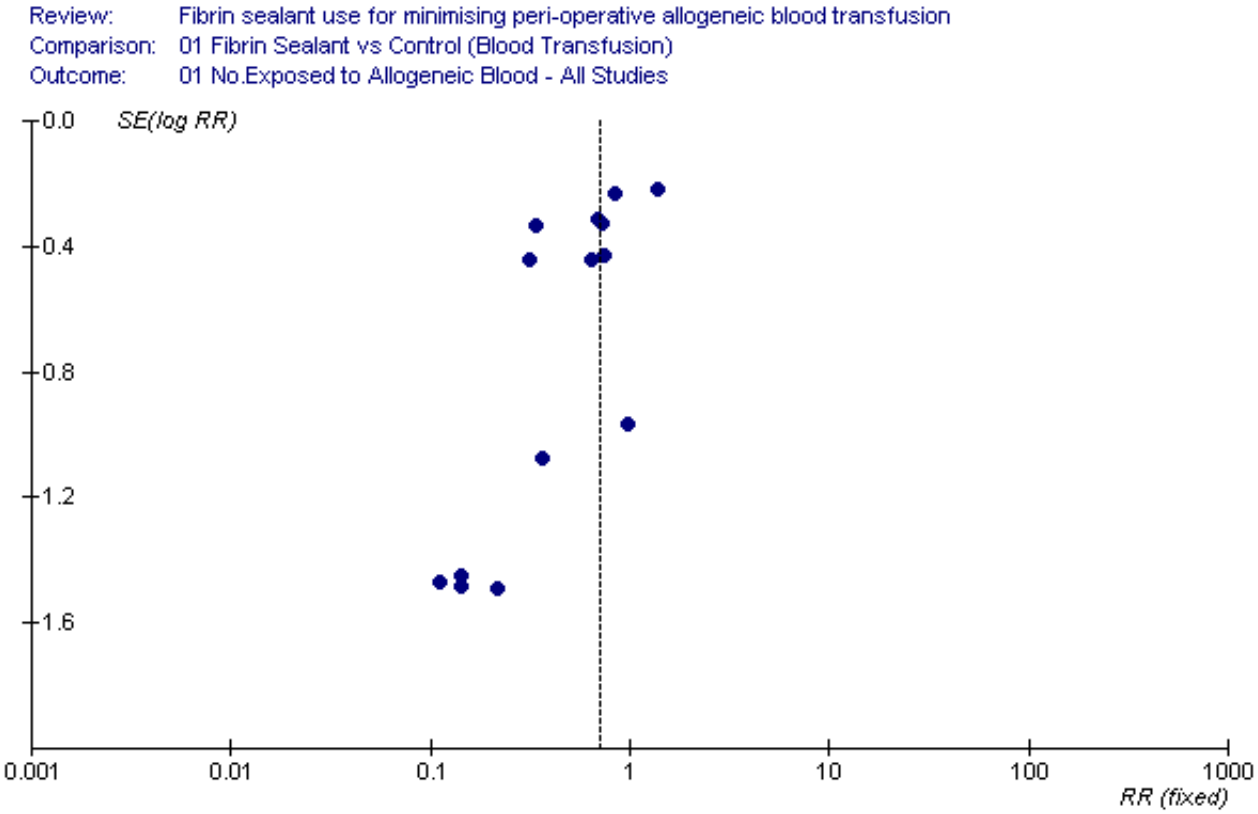
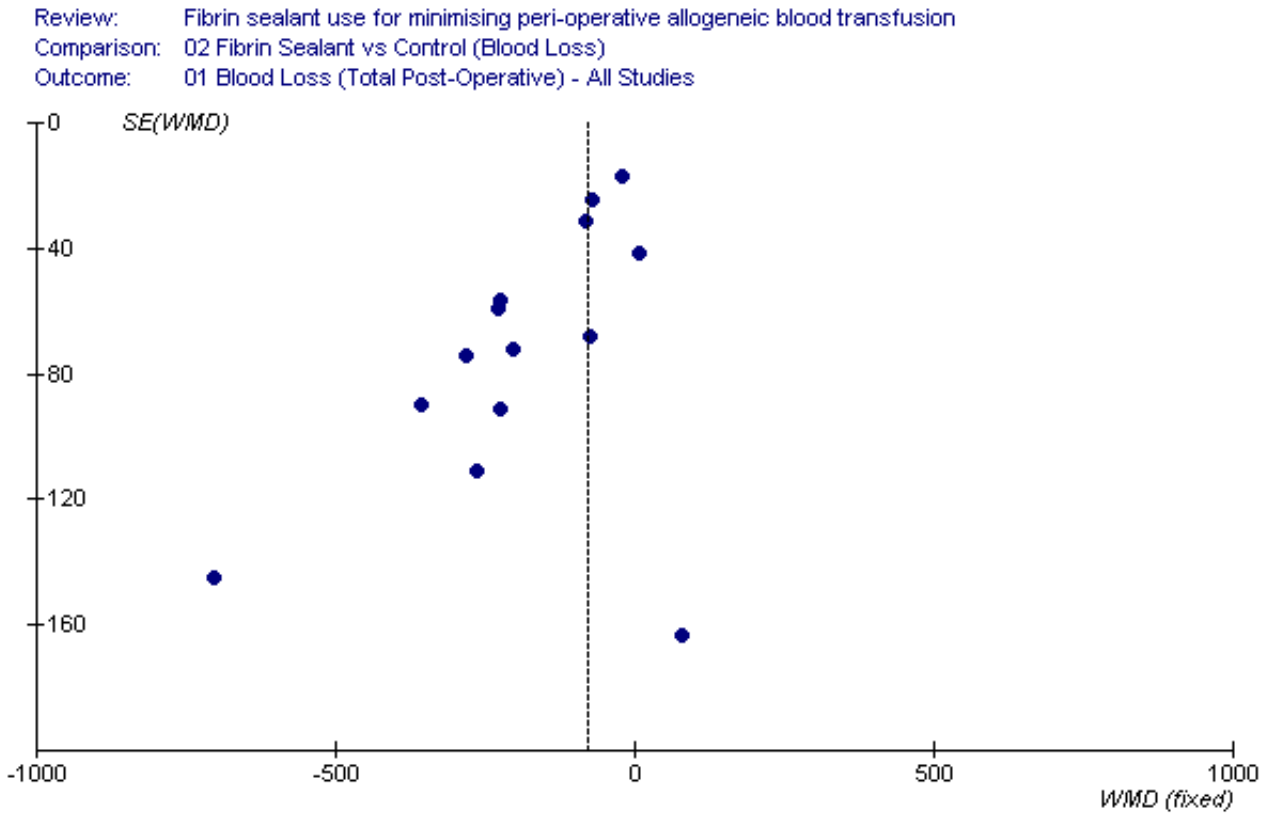


Figure 4.



In the trials reviewed here, the most significant degree of heterogeneity was found in the analysis of post-operative blood loss ($P < 0.00001$; $I^2 = 82.3\%$). Generally the observed variation was in terms of size and not the direction of effect, with data from 10 of 14 trials showing that the use of fibrin sealant statistically significantly reduced post-operative blood loss. No trial reported that fibrin sealant treatment was statistically significantly less effective than control.

To explain the variation in treatment effect, a number of factors were considered including the type of surgery, the timing of blood loss measurement, the type of fibrin sealant used, and the methods used to measure blood loss. However, with the exception of the type of surgery, subgroup analysis was severely constrained by the small number of trials. In the case of allogeneic blood transfusion, stratification of trial data by the type of surgery dramatically reduced the degree of heterogeneity ($P = 0.45$; $I^2 = 0\%$). However, in the case of post-operative blood loss, stratification of the data by the type of surgery appeared to reduce the degree of heterogeneity, but it still remained statistically significant ($P < 0.1$) for each of the four subgroups.

Trial methodological quality

The methodological quality of the trials was particularly poor with less than half of the trials assessed for methodological quality reporting the method used to generate the allocation sequence. Full blinding of outcomes assessment did not occur in any study. Only one trial (Levy 1999) used a method of concealing treatment allocation that was judged to be adequate, and 91% of the trials scored 4 or less out of a maximum score of 7 when assessed using the Schulz criteria.

This review like previous systematic reviews (Carless 2002) revealed a lack of large, well-conducted, randomised controlled trials of fibrin sealant. Only one trial included more than 100 patients in each trial arm (Figueras 2007). The current widespread usage of this agent is, therefore, not firmly supported by the available evidence. Although this review represents an important summary of the evidence, the overall results are constrained by the paucity of well-conducted studies of the efficacy of fibrin sealant, defined by reduced blood loss or reduced need for blood transfusion. As the studies reviewed here provided inadequate data for firm conclusions to be drawn about the impact of fibrin sealant use on clinically important endpoints, and given the uncertain generalisability of the results across different clinical settings and different fibrin sealants, further research involving large, methodologically rigorous, randomised controlled trials is recommended.

AUTHORS' CONCLUSIONS

Implications for practice

As an adjunct to surgical sutures, fibrin sealants appear to have a place in reducing operative blood loss; however, firm clinical evidence to support this premise is lacking. As interventions other than fibrin sealants have been shown to be effective in reducing surgical blood loss and the need for allogeneic blood transfusion (Henry 2007), the clinical decision to use fibrin sealants needs

special consideration as in many instances the risks of exposure to fibrin sealants, particularly those prepared from pooled random-donor plasma, may outweigh the benefits. With more stringent donor screening, advances in virucidal treatment processes, and the use of autologous plasma, the risks of disease transmission via fibrin sealants will be further reduced. Other risk reduction measures, such as the replacement of bovine thrombin with human-derived thrombin, and the use of tranexamic acid and epsilon aminocaproic acid (synthetic anti-fibrinolytics) in place of aprotinin (a bovine-derived anti-fibrinolytic) will further impact on the rates of adverse reactions and the potential for prion-related disease transmission (new variant Creutzfeldt Jakob disease) associated with the use of such bovine-derived products. Although recombinant technology may be the future direction as a means of producing a more globally acceptable product, the quality of autologous fibrin sealants has improved and they appear to offer a safe and comparatively effective product.

As the currently available commercial fibrin sealants are not cheap, and are associated with greater risks of disease transmission than autologous fibrin sealants, the decision to choose one product over another needs to be weighed against the potential benefits, harms, and costs of each alternative. The latter is particularly important as the majority of commercially available fibrin sealants are expensive and the commitment of extra resources within a capped health care budget may have an 'opportunity cost' in that resources are not available for more effective interventions that might bring greater benefits to a greater number of patients.

Implications for research

In view of the trials identified by this systematic review, there remains a considerable need for large, well-conducted, randomised controlled trials of fibrin sealant in elective adult surgery. To determine more accurately the impact that fibrin sealants have on peri-operative blood loss and allogeneic red blood cell (RBC) transfusion, and to provide more definitive evidence, future trials should be performed using well-defined transfusion guidelines and collect data on clinically important endpoints. Future trials also need to collect, and report separately, blood loss volumes for both the intra-operative and post-operative periods and not merely report total peri-operative blood loss. Data for allogeneic RBC transfusion needs to be collected and reported in terms of the number of patients transfused (or the proportion of patients exposed to allogeneic RBC transfusion) and the volume of blood transfused, for both the intra-operative and post-operative periods.

At present there are insufficient data to allow a definitive conclusion that one fibrin sealant is superior to another in achieving haemostasis and reducing allogeneic RBC transfusion. As the use of fibrin sealants in elective adult surgery will be influenced by availability and cost, future trials should also incorporate economic evaluations into the study design to determine the cost effectiveness of the various agents.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Belboul 2004

Methods	Patients were assigned to either the control or fibrin sealant groups by opening a sealed envelope that contained the randomisation code (allocated by a computer-generated random sequence). The personnel recording data were blinded to the intervention received. No patients were withdrawn from the study.
Participants	40 patients undergoing elective lobectomy were randomly allocated to 1 of 2 groups: (1) Fibrin sealant (n = 20), M/F = 9/11, mean age (+/-SD) = 63.2 (12.8) years (2) Control group (n = 20), M/F = 11/9, mean age (+/-SD) = 65.3 (9.9) years
Interventions	(1) Fibrin sealant group donated 120 ml of whole blood which was processed by the Vivostat® system. Fibrin sealant was applied over all areas at risk of air leaks and bleeding (all areas of dissection) with the lung deflated and without ventilation. (2) Control group received standard care (no fibrin sealant was used).
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Blood loss (ml) - 24-hour post-operative + total. Length of hospital stay (days). Air leakage (n). Days with drain.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated random sequence
Allocation concealment?	High risk	C - Inadequate (sealed envelopes contained randomisation code)
Blinding? All outcomes	Low risk	Outcomes assessed blind

Fabian 2003

Methods	At the conclusion of the resection patients were randomly assigned in the operating room to control or treatment group in a 1:1 ratio by opening a sealed envelope. Upon arrival in the recovery room each patient was assessed by the blinded observer. During the subsequent 48 hours the blinded observer recorded the data every 8 hours. The method used to generate random sequences was not described.

Fabian 2003 *(Continued)*

Participants	100 patients undergoing elective lobar and wedge pulmonary resections were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 50), M/F = 25/25, mean age (range) = 68 (52 to 85) years. (2) Control group (n = 50), M/F = 23/27, mean age (range) = 66 (20 to 87) years.
Interventions	(1) Fibrin sealant group received an application of 5 ml of fibrin glue using the HemaMyst® system. A fine aerosolised mist spray of fibrin glue was applied. Raw and stapled lung surfaces were sprayed with a portion of the fibrin glue. This spray was followed by the application of fibrin glue to the mediastinal lymph node bed when applicable and then spraying the remainder of fibrin glue on the dissected or stapled lung and bronchial stump. (2) Control goup did not receive fibrin sealant treatment.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Blood loss (ml) - 24 hours post-operative. Wound infection (n). Length of hospital stay (days). Prolonged air leaks (n). Alveolar air leaks (n). Empyema (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	High risk	C - Inadequate (sealed envelopes were used)
Blinding? All outcomes	Low risk	Outcomes assessed blind

Figueras 2007

Methods	Randomisation was performed using sealed envelopes and was stratified to include similar numbers of cirrhotic patients in each study. Data were analysed on the intention-to-treat principle.
Participants	300 patients undergoing elective hepatectomy were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 150), M/F = 59/91, mean age (+/-SD) = 62 (11) years. (2) Control group (n = 150), M/F = 46/104, mean age (+/-SD) = 60 (11) years.
Interventions	(1) Fibrin sealant group received 5 mls of Tissucol® in aerosolised form on the raw surface of the liver with an absorbable collagen sponge also applied with manual pressure after spraying the glue. (2) Control group received neither the fibrin sealant nor the collagen sponge.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Amount of allogeneic blood transfused (units). Blood loss.
Notes	

Risk of bias

Figueras 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	High risk	C - Inadequate (sealed envelopes were used)
Blinding? All outcomes	Unclear risk	Not reported

Gasser 1983

Methods	Methods of randomisation and allocation concealment were not described. Blinding was not described.
Participants	110 patients undergoing elective suprapubic prostatectomy were allocated to 1 of 3 groups: (1) Fibrin sealant + collagen fleece group (n = 44). (2) Collagen fleece group (n = 28). (3) Control group (n = 38). NB: Mean age of the participants was 71.3 years (range 55 to 85 years).
Interventions	(1) Fibrin sealant + collagen fleece group had the prostatic cavity closed by instilling FS into the cavity and subsequently had collagen fleece introduced into the cavity spread around the balloon of a balloon catheter. (2) Collagen fleece group were treated with the use of collagen fleece alone with no FS treatment. (3) Control group were not treated with either FS or collagen fleece.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Blood loss (ml) - total post-operative estimated blood loss. Wound healing (n). Length of hospital stay (days). Pre/post-operative Hb + Hct levels. Complications (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Jackson 1999

Methods	Sealed envelopes were used to conceal treament allocation. Randomisation was performed using a random number table. Blinding was not described.

Jackson 1999 *(Continued)*

Participants	47 patients undergoing elective carotid endarterectomy and expanded polytetrafluoroethylene carotid patch angioplasty were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 24), M/F = 15/9. (2) Control group (n = 23), M/F = 18/5. NB: Mean age (+/-SD) age of the participants was 67.7 (6) years.
Interventions	(1) Fibrin sealant group were treated with solvent-detergent treated human FS (Baxter Healthcare) containing purified human fibrinogen and purified human thrombin. The FS was applied as a liquid using a dual syringe technique with 3 ml of each of the two main components (fibrinogen and thrombin). (2) Control group were treated with thrombin-soaked gelatin (TSG) sponge (Gelfoam, Upjohn). The Gelfoam was cut into 1.0 x 3.0 cm strips before application. Bovine thrombin solution was applied to the wafers of the Gelfoam.
Outcomes	Blood loss (ml) - intra-operative estimated blood loss. Time to haemostasis (min). Stroke (n). Wound complications (n). Pre-post Hb levels. Transient ischemic attacks (n). Mortality (n). Biochemical data.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random number table
Allocation concealment?	High risk	C - Inadequate (sealed envelopes)
Blinding? All outcomes	Unclear risk	Not reported

Kjaergard 1998

Methods	Methods of randomisation and allocation concealment were not described. Study was described as being single-blinded.
Participants	24 patients undergoing elective primary coronary artery bypass surgery were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 12). (2) Control group (n = 12). NB: Mean age of the participants was 62.4 years (range = 44 to 77 years); M/F = 22/2.
Interventions	(1) Fibrin sealant group received autologous FS, obtained using the Vivostat® system, applied with a spray system at the end of the operation, after reversal of heparin with protamine. FS was applied at any bleeding sites after conventional haemostasis was performed. Additionally it was applied at the anastomoses, the mammary pedicle, the mediastinum, and the sternal marrow. (2) Control group received conventional haemostasis only. No FS was used. NB: All patients received 3 drains: a pericardial drain, a retrosternal drain, and a left pleural drain. Autotransfusion of shed mediastinal and pleural blood was used post-operatively for all patients.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n).

Kjaergard 1998 *(Continued)*

	Blood loss (ml). Mortality (n). Adverse events (n). Re-operation due to bleeding (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	High risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	High risk	Single blind - patients only

Kohno 1992

Methods	Method of randomisation was not described. Sealed envelopes were used to conceal treatment allocation. Blinding was not described.
Participants	62 patients undergoing elective hepatic resection were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 31), M/F = 25/6, mean age (+/-SD) = 63 (8) years. (2) Control group (n = 31), M/F = 23/8, mean age (+/-SD) age = 60 (9) years.
Interventions	(1) Fibrin sealant group: during parenchymal dissection in major and minor resections, vessels and bile ducts were hemo-clipped or ligated meticulously. Small surgical bleeding and haemorrhage from the vessels withdrawn into the parenchyma were managed with mattress sutures, with or without electrocauterisation. After those procedures, soft sterile paper was placed on the cut surface to measure the cut area. FS (Beriplast P®) was then applied onto the cut surface of the liver using a syringe. (2) Control group: the cut surface of the liver was treated with microcrystalline collagen powder (Avitene®). The wound was then pressed tightly with a gauze sponge every 5 minutes.
Outcomes	Blood loss (ml) - 24 hours post-operative. Blood loss (ml) - total blood loss. Blood loss (ml) - intra-operative. Intra-operative haemostatic efficacy. Bile leakage (n). Post-operative re-bleeding (n). Complications (n). Mortality (n). Wound infection (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	High risk	C - Inadequate (sealed envelopes)

Kohno 1992 *(Continued)*

Blinding? All outcomes	Unclear risk	Not reported

Lassen 2006

Methods	When patients arrived in the operating suite an evelope was opened which contained details of the allocated treatment group (a computer-generated random sequence was used).
Participants	80 patients undergoing elective primary hip arthroplasty were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 33), M/F = 12/21, mean age (+/-SD) = 67.1 (8.9) years. (2) Control group (n = 36), M/F = 15/21, mean age (+/-SD) = 63.1 (10.9) years. NB: 11 patients randomised to the fibrin sealant group were excluded from the analysis as no fibrin sealant was applied during surgery as intended. Reasons for exclusion included: machine malfunctions, operator errors, not producing the fibrin on time, and forgetting to apply the sealant.
Interventions	(1) Fibrin sealant group donated 120 ml of whole blood which was then processed peri-operatively using the Vivostat® system to produce fibrin sealant. The Vivostat-derived sealant was applied to the bleeding surgical wound surfaces after an appropriate attempt to dry the surface before application of Vivostat before closure, in an attempt to stop or prevent bleeding. The surgeons were asked to dry the surface to which the Vivostat was to be sprayed as much as possible before application. (2) Control group received no fibrin sealant or additional haemostatic treatment.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Amount of allogeneic blood transfused (ml). Blood loss (ml) - intra-operative. Length of hospital stay (days). Auto-transfusion (n) - cell salvage. Haematoma (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated random sequence
Allocation concealment?	High risk	C - inadequate (sealed envelopes)
Blinding? All outcomes	High risk	Open-label study

Levy 1999

Methods	Randomisation was determined according to patient number, which had been assigned with a computer-generated randomisation list. Randomisation was centralised.
Participants	58 patients undergoing elective total knee arthroplasty were randomly divided into 1 of 2 groups: (1) Fibrin sealant group (n = 29), M/F = 6/23, mean age (+/-SD) age = 68.9 (6.3) years. (2) Control group (n = 29), M/F = 6/23, mean age (+/-SD) age = 70.2 (8.2) years.
Interventions	(1) Fibrin sealant group received 10 to 20 ml of Quixil® (octacol F15, Omrix Biopharmaceuticals) applied by topical spraying with the use of a double-syringe spray-device. The FS was sprayed over the tissues,

Levy 1999 *(Continued)*

	into the joint itself, on the raw surfaces of the bones, on the muscles and tendons, and around the subcutaneous tissues. (2) Control group received no FS treatment. Conventional haemostatic measures were used. NB: All operations were performed in a bloodless field with the use of a pneumatic tourniquet. Electrocautery of the major vessels was performed. The entire operative field was thoroughly rinsed of any debris and was meticulously dried. Drains placed insitu were connected to high-vacuum suction drains.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Blood loss (ml) - apparent blood loss - post-operative drainage. Blood loss (ml) - total estimated post-operative blood loss. Mortality (n). Fever (n). Infection (n). Reduction in Hb and Hct levels. Haematoma development (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated randomisation list
Allocation concealment?	Low risk	A - Adequate (central randomisation)
Blinding? All outcomes	High risk	Blinding was not adequate

Lillemoe 2004

Methods	Patients were randomised using a randomly generated number pattern. Method used to conceal treatment allocation was not described. Blinding was not reported.
Participants	124 patients undergoing elective pancreaticoduodenectomy were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 58), M/F = 37/58, mean age (+/-SD) = 64 (15.2) years. (2) Control group (n = 66), M/F = 40/66, mean age (+/-SD) = 64 (16.2) years.
Interventions	(1) Fibrin sealant group received 8 ml of fibrin sealant applied through a double-barrel syringe connected to a 'y'-shaped catheter. The FS was applied circumferencially to the entire anastomosis after the completion of all 3 anastomosis. (2) Control group did not receive fibrin sealant treatment.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Blood loss (ml). Mortality (n). Wound infection (n). Re-operation (n). Length of hospital stay (days). Pancreatic fistula (n).
Notes	

Risk of bias

Lillemoe 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Random number generator
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Liu 1993

Methods	Methods of randomisation and allocation concealment were not described.
Participants	40 patients undergoing elective liver resection were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 20), M/F = 19/1, mean age (+/-SD) = 55 (13.7) years. (2) Control group (n = 20), M/F = 18/2, mean age (+/-SD) = 64.5 (9.8) years.
Interventions	(1) Fibrin sealant group: at the end of liver resection, when the bleeding had been checked, the raw surface area was measured by first applying a gauze over the cut surface, then measuring the blood tinged gauze. FS was then applied to the raw surface by means of a double-barrelled syringe then the wound was closed with a Jackson-Pratt closed system drain left in the subphrenic or subhepatic space. (2) Control group: received no FS treatment.
Outcomes	Blood loss (ml) - intra-operative blood loss. Blood loss (g) - estimated post-operative blood loss. Drainage (days). Secondary bleeding (n). Pleural effusion (n). Bile leakage (n). Wound infection (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	High risk	Outcomes assessment was not blinded

Lobato 2001

Methods	Method of randomisation and allocation concealment were not described. Blinding was not described.
Participants	60 patients undergoing elective incisional hernia repair with associated dermolipectomy were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 30), M/F = 2/28, mean age (range) = 56.9 (28 to 74) years.

Lobato 2001 *(Continued)*

	(2) Control group (n = 30), M/F = 2/28, mean age (range) = 49.6 (32 to 72) years.
Interventions	(1) Fibrin sealant group received a vapourisation of Tissucol® fibrin sealant with a Tissomat® mechanism and Duplojet® system was applied over the subcutaneous tissue and muscle layer after haemostasis was achieved. The average amount of Tissucol® applied was 1.9 ml per patient (range = 1 to 4 ml/patient). A total of 55 ml was used in all patients. (2) Control group received standard treatment. No fibrin sealant was used.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Amount of allogeneic blood transfused (units). Respiratory infection (n). Wound infection (n). Length of hospital stay (days). Haematoma (n). Seroma formation (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Luke 1986

Methods	Method of randomisation and allocation concealment were not described. Blinding was not described.
Participants	30 patients undergoing elective transurethral prostatectomy (TURP) for presumed benign prostatic hypertrophy (BPH) were randomised to 1 of 2 groups: (1) Fibrin sealant group (n = 15). (2) Control group (n = 15). NB: Median age of the participants was 73 years (range = 52 to 92 years).
Interventions	(1) Fibrin sealant group: a device was constructed for applying fibrin glue into the prostatic cavity by attaching a ureteric catheter (No.6) to a 2-balloon urethral catheter (Silicolatex Rusch No.22) between the balloons. The catheter was inserted into the bladder. Water (50 ml) was instilled into balloon B and the catheter retracted into the correct position, ensuring the openings of the ureteric catheter were placed in the resected prostatic cavity. Fibrinogen solution (2 ml) was injected through the ureteric catheter and balloon A was inflated with air to disperse the solution over the walls of the cavity. Balloon A was then deflated and the thrombin solution was injected. Balloon A was reinflated for a period of 5 minutes, then deflated. (2) Control group: received no FS treatment.
Outcomes	Blood loss (mls) - estimated post-operative blood loss (72 hours). Complications (n). Infection (n).
Notes	

Luke 1986 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Mawatari 2006

Methods	Patients were randomised to intervention or control by means of a computer-generated randomisation list. Blinding was not described. Method used to conceal treatment allocation was not described.
Participants	100 female patients undergoing elective total hip arthroplasty were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 50), mean age (+/-SD) = 60 (11) years. (2) Control group (n = 50), mean age (+/-SD) = 60 (10) years.
Interventions	(1) Fibrin sealant group: whole blood was collected and centrifuged. Separated plasma was collected and stored at -40 °C and then thawed by storage at 4 °C for 24 hours. The freeze-and-thaw process was repeated twice. The plasma was centrifuged after the second thawing and an autologous cryoprecipitate (auto-Cryo) was obtained. The auto-Cryo was stored at -40 °C and thawed just prior to surgery (Solution A). Solution A was delivered to the operating room where Solution B (thrombin 5000 IU, 5 ml of 2% calcium chloride, aprotinin 50,000 IU) was prepared. Solutions A and B were individually filled into a double-syringe spray device and used as auto-FTA. The volume auto-FTA (autologous fibrin sealant) was approximately 10 ml. (2) Control group: received standard treatment without fibrin sealant treatment.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Blood loss (ml) - total blood loss. Blood loss (ml) - 24 and 48 hours post-operative blood loss. Infection (n). Deep venous thrombosis (n). Pulmonary embolus (n).
Notes	All patients were able to donate 400 ml of whole blood 3 weeks prior to surgery without the need for erythropoietin (EPO). Patients then received oral iron supplements (200 mg ferrous fumarate) for 3 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated randomisation
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Milne 1995

Methods	Method of allocation concealment and blinding were not described. Patients were randomised using computer-generated sequences.
Participants	17 patients undergoing elective carotid endarterectomy were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 8). (2) Control group (n = 9). NB: Mean age of the participants was 64.5 years (range = 48 to 75 years).
Interventions	(1) Fibrin sealant group: following completion of the vascular anastomosis fibrin sealant was applied to the suture line using a dual syringe technique. (2) Control group: received no FS treatment.
Outcomes	Blood loss (ml) - intra-operative blood loss. Re-operation for bleeding (n). Stroke (n). Time to haemostasis (min). Number of patients requiring extra haemostasis treatment (n). Wound complications (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer-generated random sequence
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Molloy 2007

Methods	Patients were randomised using a block design with permutated block of 5, which was concealed until interventions were assigned. All patients completed follow up. All the patients and staff, except those directly administering the fibrin sealant, were blinded to the treatment, including those assessing and collecting the post-operative measurements, investigations and outcomes.
Participants	150 patients undergoing elective total knee replacement were randomly allocated to 1 of 3 groups: (1) Fibrin sealant group (n = 50). (2) Tranexamic acid group (n = 50). (3) Control group (n = 50). NB: Demographic data not reported.
Interventions	(1) Fibrin sealant group received 10 mls of reconstituted fibrin sealant (Quixil; Johnson & Johnson Wound Management, Somerville, New Jersey, US) intra-operative with 6 ml sprayed on to the posterior capsule and surrounding soft tissues before the prosthesis was inserted, and the remaining 4 ml sprayed onto the bone which was exposed after placement of the prosthesis and on the soft tissues after closure of the capsule. (2) Tranexamic acid group received 500 mg of intravenous TXA 5 minutes before deflation of the tourniquet and a repeat dose 3 hours later. (3) Control group received no pharmacological intervention.

Molloy 2007 *(Continued)*

Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Amount of allogeneic blood transfused (units). Blood loss (ml) - total blood loss. Mortality (n). Wound infection (n). Length of hospital stay (days). Deep venous thrombosis (n). Pulmonary embolus (n).
Notes	All patients received 150 mg of aspirin (ASA) as a single dose the evening before surgery and daily for 6 weeks post-operatively.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	High risk	Outcomes were assessed blind

Noun 1996

Methods	Method of randomisation and allocation concealment were not described. Blinding was not described.
Participants	82 patients undergoing elective liver resection were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 38), M/F = 24/14, mean age (+/-SD) = 52 (15) years (2) Control group (n = 44), M/F = 20/24, mean age (+/-SD) = 49 (15) years
Interventions	(1) Fibrin sealant group: liver transection was performed using Kelly forceps and ultrasonic dissector, which isolated vascular and biliary radicles. Haemostasis was secured by sutures and clips. At peritoneal closure after the completion of haemostasis and biliostasis, a single dose of FS (Biocol®) was applied to the liver cut surface. A silicone rubber closed-system drain was placed in the empty space created by the removal of the liver parenchyma. (2) Control group: received no fibrin sealant treatment.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Amount of allogeneic blood transfused (units). Total fluid drainage (ml) - 72 hours post-operative. Infection (n). Hb and bilirubin concentration of fluid drainage. Length of hospital stay (days). Operation time (hours). Ascites (n). Subphrenic collections (n). Pulmonary complications (n).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Noun 1996 *(Continued)*

Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Shah 2006

Methods	Patients were allocated to treatment based on a balanced, block randomisation process with a block size of 6 patients. When a patient met all criteria, a sealed envelope was opened in sequence and the patient was accordingly allocated to a group. Participants were not blinded. One patient crossed over from the control to the experimental group after group allocation was revealed. This patient was excluded from the analysis.
Participants	63 patients undergoing elective percutaneous nephrolithotomy were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 32), M/F = 22/10, mean age (+/-SD) = 45.63 (11.96) years. (2) Control group (n = 31), M/F = 19/12, mean age (+/-SD) = 45.55 (13.02) years.
Interventions	(1) Fibrin sealant group: a Duplotip applicator was loaded with 2 ml of Tisseel fibrin sealant, which was then introduced through the working channel of the nephroscope. The entire assembly was gradually withdrawn until the applicator tip was just below the renal capsule. Intra-irrigation was stopped at this point to prevent the entry of fibrin glue into the pelvicaliceal system. The fibrin sealant was gradually injected into the nephrostomy tract and the Amplatz sheath was simultaneously withdrawn. The skin incision was left unsutured and strapped with a pressure dressing. (2) Control group: after complete stone clearance was confirmed fluroscopically and endoscopically a 6 Fr Double-J stent was placed in antegrade fashion. The Amplatz sheath was removed and the wound strapped with a pressure dressing.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Septicaemia (n). Length of hospital stay (days). Mild haematuria (n). Urethral catheterisation (n). Post-operative fever (n). Urinary retention (n).
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	High risk	C - Inadequate (sealed envelopes)
Blinding? All outcomes	Unclear risk	Not reported

Sintler 2005

Methods	Patients were randomised at the time of completion of the patch reconstruction to receive 1 of 2 study products by means of previously prepared sealed envelopes. The surgeon remained blind to the treatment allocation until this point. No patients were excluded during the study.
Participants	20 patients undergoing elective carotid endarterectomy with ePTFE patch reconstruction were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 10), M/F = 7/3, mean age (range) = 71.1 (62 to 89) years. (2) Control group (n = 10), M/F = 7/3, mean age (range) = 71.1 (64 to 82) years.
Interventions	(1) Fibrin sealant group were treated with Quixil® supplied as 2 vials each containing 5 mls of product (biologic activated component (BAC) or thrombin). A maximum of 10 ml of combined product was available for each patient. Once applied only light pressure from a surgical swab was used to absorb any exuded blood - so not to disturb the seal. (2) Control group were treated with Kaltostat® which is a soft, white, sterile non-woven dressing of calcium sodium alginate fiber (80% calcium, 20% sodium). On contact with a wound, Kaltostat absorbs wound exudates, and the calcium ions in the dressing are exchanged with sodium ions in the exudates, which causes the dressing to transform from a dry dressing into a firm moist gel. Kaltostat was applied to the suture line as 7 x 12 cm sheets. Local pressure was applied.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Amount of allogeneic blood transfused (units). Blood loss (ml). Mortality (n). Drainage (ml). Stroke (n). Transient ischemic attack (n). Pulmonary embolus (n). Time to haemostasis (min).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	High risk	C - Inadequate (sealed envelopes)
Blinding? All outcomes	High risk	Blinding was not adequate

Stutz 2004

Methods	Methods of randomisation and allocation concealment not described. Abstract only.
Participants	21 patients undergoing elective total knee arthroplasty were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 10). (2) Control group (n = 11). NB: Demographic data not reported.
Interventions	(1) Fibrin sealant group received 15 to 16 ml of autologous fibrin glue (CryoSeal® FS) sprayed on the surfaces of the wound. To obtain the autologous fibrin sealant 600 ml of whole blood was collected and subsequently separated into plasma and red blood cells. The red cell concentrate was re-transfused to the donor. The FS components - cryoprecipitate and thrombin were produced from platelet-poor

Stutz 2004 *(Continued)*

	plasma using the Cryoseal FS system. From each production cycle, active thrombin and cryoprecipitate were collected in three pairs (16 mls) of sterile over-wrapped syringes and were stored frozen at -80 °C until just before use. (2) Control group received standard care with haemostasis performed by diathermy.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Amount of allogeneic blood transfused (units). Blood loss (ml) - total blood loss. Blood loss (ml) - post-operative blood loss.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Taylor 2003

Methods	Multi-centre (26 medical centres), randomised, single-blinded trial (study personnel could not be blinded to the nature of the experimental versus control treatment). Sealed envelopes contained randomisation codes/schedule. Data for 1 of 201 randomised subjects were excluded from intention-to-treat analysis because surgery was aborted before completion of the vascular graft. This left 200 randomised subjects with data analysed with the intention-to-treat method. Of these 199 actually received study treatment. There was no treatment crossover.
Participants	201 patients undergoing elective femoral artery grafts were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 101), M/F = 64/37, mean age = 65 years. (2) Control group (n = 99), M/F = 61/38, mean age = 63 years.
Interventions	(1) Fibrin sealant group received Beriplast® P fibrin sealant. Solution A (human fibrinogen 65 to 115 mg; Factor XIII 40 to 80U; human albumin 5 to 15 mg; aprotinin 100 KIU/ml) and Solution B (thrombin 400 to 600 IU; calcium chloride 40 mmol) were reconstituted and drawn into 2 syringes. These 2 syringes were mounted into a device (Pantaject®; Aventis Behring) that allowed simultaneous mixing and application. (2) Control group received thrombin-soaked gelatin sponge (TSG). The TSG was cut into appropriate sized rectangles and soaked in thrombin solution before randomisation. After randomisation TSG was applied to the anastomosis followed by manual pressure within 20 seconds with gauze (4 cm x 4 cm) surgical sponges and the arterial clamps were released. The intervals between release of sponge pressure to observe for haemostasis were left to individual surgeon judgement.
Outcomes	Blood loss (g). Mortality (n). Length of hospital stay (days). Length of ICU stay (days). Haemorrhage post-operative (n). Haemostasis at 4 min.
Notes	

Taylor 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	High risk	C - Inadequate (sealed envelopes)
Blinding? All outcomes	High risk	Single-blinded study

Uetsuji 1994

Methods	Method of randomisation and allocation concealment were not described. Blinding was not described.
Participants	64 patients undergoing elective hepatectomy with liver mobilisation were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 25), M/F = 21/4, mean age (+/-SD) = 60.4 (6.6) years. (2) Control group (n = 39), M/F = 32/7, mean age (+/-SD) = 58.2 (9.9) years.
Interventions	(1) Fibrin sealant group underwent liver mobilisation by severing the hepatic ligaments. Fibrin sealant (Tissucol®) was evenly sprayed after hepatectomy on the undersurface of the diaphragm around the insertion of the liver ligaments using a Tissomat® Duploject® spray system. (2) Control group underwent liver mobilisation by severing the hepatic ligaments but did not receive FS treatment.
Outcomes	Amount of allogeneic blood transfused (units). Amount of fresh frozen plasma transfused (ml). Blood loss (ml) - intra-operative estimated blood loss. Operation time (min). Post-operative liver function. Pleural effusion (n). Ascites formation (n) - post-operative.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Vecsey 1980

Methods	Method of randomisation and allocation concealment were not described. Blinding was not described.

Vecsey 1980 *(Continued)*

Participants	40 patients undergoing elective transvesical adenomectomy (prostatectomy) were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 20). (2) Control group (n = 20). NB: Demographic data was not reported.
Interventions	(1) Fibrin sealant group were treated by instilling fibrin sealant into the prostatic cavity and subsequently had collagen fleece introduced into the cavity spread around the balloon of a balloon catheter. (2) Control group were not treated with FS. Tamponade of the prostatic cavity was performed using balloon compression only.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Amount of allogeneic blood transfused (units). Blood loss (ml) - post-operative 24 and 96 hours.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Wang 2001

Methods	Method of randomisation and allocation concealment were not described. Blinding was not described.
Participants	53 patients undergoing elective unilateral primary total knee arthroplasty with cement were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 25), M/F = 13/12, mean age (+/-SD) = 68.5 (10.4) years. (2) Control group (n = 28), M/F = 11/17, mean age (+/-SD) age = 69.4 (8.7) years.
Interventions	(1) Fibrin sealant group: following cementing of the joint and before tourniquet deflation and wound closure, 10 mls of the virally inactivated Quixil® (Omrix Biopharmaceuticals SA) was sprayed onto the raw surfaces of the exposed bone and soft tissue using a dual-syringe spray device. Drains were then placed in situ. (2) Control group: received standard treatment without the use of fibrin sealant.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Blood loss (ml) - post-operative 24 hours. Haematoma (n). Haemoglobin levels.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Wang 2001 *(Continued)*

Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

Wang 2003

Methods	Single-blind, prospective, randomised, parallel-group, multicentre, Phase III FDA-monitored (US Food and Drug Administration) trial conducted in the US (six sites) and the UK (three sites). Patients were randomised following an intention-to-treat protocol.Randomisation was performed using permuted blocks of variable size and stratified by the surgeon. Treatment assignment was intra-operative and was revealed as late as possible by use of sealed envelopes. The investigational fibrin sealant was prepared in the operating room before the patient's assignment was revealed in order to prevent delay in its application and permit maintenance of the blinding for as long as possible.
Participants	81 patients undergoing elective total hip replacement were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 38), M/F = 22/16, mean age (+/-SD) = 66.9 (11.5) years. (2) Control group (n = 43), M/F = 23/20, mean age (+/-SD) = 67.8 (10.6) years.
Interventions	(1) Fibrin sealant group received a total of 10 ml of fibrin sealant sprayed onto the exposed tissue at 3 predetermined stages of the procedure. Routine haemostatic techniques such as cauterisation and suture ligation were used until the femoral neck was osteotomised, the acetabular exposure was carried out, and the deep acetabular retractors were placed. Approximately 4 ml of the investigational fibrin sealant was then sprayed onto the whole wound. Another 4 ml of FS was sprayed primarily onto the deep tissues around the acetabulum after the acetabular component was inserted, any acetabular osteophytes were removed, and all peri-acetabular soft tissue resection was completed. The final 2 ml of FS was sprayed after any deep repair but before closure of the fascia. (2) Control group received standard (usual) care with no fibrin sealant.
Outcomes	Number of patients exposed to allogeneic blood transfusion (n). Blood loss (ml) - intra-operative/post-operative estimated blood loss. Blood loss (ml) - total estimated blood loss. Length of hospital stay (days). Anaemia (n). Seroconversion (n). Change in Hb level.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	High risk	C - Inadequate (sealed envelopes)
Blinding? All outcomes	Unclear risk	Not reported

Wurtz 1991

Methods	Method of randomisation and allocation concealment were not described. Blinding was not described.
Participants	50 patients undergoing elective partial pulmonary excision were randomly allocated to 1 of 2 groups: (1) Fibrin sealant group (n = 25). (2) Control group (n = 25). NB: Mean age of the participants was 52 years (range = 15 to 71 years); M/F = 42/8.
Interventions	(1) Fibrin sealant group: haemostasis and aerostasis of the fissural and/or intersegmentary dissection planes were achieved by the use of FS (Biocol®) prepared by the Central Regional Transfusion Service of Lille, France. FS was administered by the use of a dual-syringe system. (2) Control group: haemostasis and aerostasis of the fissural and/or intersegmentary dissection planes were achieved by the use of electrocoagulation.
Outcomes	Blood loss (ml) - total blood loss. Blood loss (ml) - 24 hours post-operative. Faulty re-expansion (n). Quality of aerostasis. Number of patients requiring repeat drainage (n). Length of hospital stay (days).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Method of randomisation was not reported
Allocation concealment?	Unclear risk	B - Unclear
Blinding? All outcomes	Unclear risk	Not reported

FS = fibrin sealant
TXA = tranexamic acid
Hb = haemoglobin
Hct = haematocrit

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Courtade 1996	Active versus active comparison. All trial arms treated with fibrin sealant.
Shiono 1998	Active versus active comparison. Both trial arms treated with fibrin sealant.

DATA AND ANALYSES

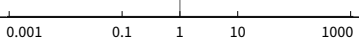
Comparison 1. Fibrin sealant versus control (blood transfusion)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No. exposed to allogeneic blood - all studies	18	1406	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.88]
2 No. exposed to allogeneic blood - type of surgery	18	1406	Risk Difference (M-H, Random, 95% CI)	-0.07 [-0.13, -0.02]
2.1 Orthopaedic surgery	7	482	Risk Difference (M-H, Random, 95% CI)	-0.14 [-0.30, 0.03]
2.2 Prostate surgery	2	112	Risk Difference (M-H, Random, 95% CI)	-0.27 [-0.55, 0.01]
2.3 Liver surgery	2	382	Risk Difference (M-H, Random, 95% CI)	0.02 [-0.11, 0.15]
2.4 Pancreatic surgery	1	124	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.03, 0.03]
2.5 Thoracic surgery	2	140	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.04, 0.04]
2.6 Vascular surgery	1	20	Risk Difference (M-H, Random, 95% CI)	-0.3 [-0.60, 0.00]
2.7 Kidney surgery	1	63	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.12, 0.12]
2.8 Cardiac surgery	1	23	Risk Difference (M-H, Random, 95% CI)	-0.16 [-0.46, 0.14]
2.9 Incisional hernia repair	1	60	Risk Difference (M-H, Random, 95% CI)	-0.13 [-0.27, -0.00]
3 No. exposed to allogeneic blood - transfusion protocol	18	1406	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.88]
3.1 Transfusion protocol	4	481	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.28, 1.49]
3.2 No transfusion protocol	14	925	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.46, 0.83]
4 No. exposed to allogeneic blood - type of fibrin sealant	18	1406	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.88]
4.1 Quixil - commercial fibrin sealant	5	312	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.41, 0.84]
4.2 Tisseel/Tissucol/Hemaseel - commercial fibrin sealant	7	759	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.19, 1.50]
4.3 Biocol - commercial fibrin sealant	1	82	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.32, 1.71]
4.4 CryoSeal FS - autologous fibrin sealant	1	21	Risk Ratio (M-H, Random, 95% CI)	0.22 [0.01, 4.06]
4.5 'Home-made' - autologous fibrin sealant	1	100	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.6 Vivostat system - autologous fibrin sealant	3	132	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.52, 1.24]
5 No. exposed to allogeneic blood - methodological quality	18	1406	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.45, 0.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Quality A	1	58	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.13, 0.74]
5.2 Quality B	10	675	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.37, 0.74]
5.3 Quality C	7	673	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.63, 1.36]
6 Units of allogeneic blood transfused - all studies	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 Units of allogeneic blood transfused - all studies	8	685	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.54, -0.01]

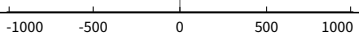
Analysis 1.1. Comparison 1 Fibrin sealant versus control (blood transfusion), Outcome 1 No. exposed to allogeneic blood - all studies.

Study or subgroup	FS n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Belboul 2004	0/20	0/20			Not estimable
Fabian 2003	0/50	0/50			Not estimable
Figueras 2007	40/150	29/150		15.15%	1.38[0.91,2.1]
Gasser 1983	9/44	17/28		11.25%	0.34[0.18,0.65]
Kjaergard 1998	1/11	3/12		2.19%	0.36[0.04,3]
Lassen 2006	16/33	21/36		14.69%	0.83[0.53,1.3]
Levy 1999	5/29	16/29		8.5%	0.31[0.13,0.74]
Lillemoe 2004	0/58	0/66			Not estimable
Lobato 2001	0/30	4/30		1.24%	0.11[0.01,1.98]
Mawatari 2006	0/50	0/50			Not estimable
Molloy 2007	7/50	11/50		8.5%	0.64[0.27,1.51]
Noun 1996	7/38	11/44		8.73%	0.74[0.32,1.71]
Shah 2006	2/32	2/31		2.65%	0.97[0.15,6.46]
Sintler 2005	0/10	3/10		1.27%	0.14[0.01,2.45]
Stutz 2004	0/10	2/11		1.21%	0.22[0.01,4.06]
Vecsey 1980	0/20	3/20		1.22%	0.14[0.01,2.6]
Wang 2001	9/25	14/28		11.46%	0.72[0.38,1.37]
Wang 2003	11/38	18/43		11.94%	0.69[0.38,1.27]
Total (95% CI)	**698**	**708**		**100%**	**0.63[0.45,0.88]**
Total events: 107 (FS), 154 (Control)					
Heterogeneity: Tau^2=0.14; Chi^2=23.76, df=13(P=0.03); I^2=45.29%					
Test for overall effect: Z=2.74(P=0.01)					



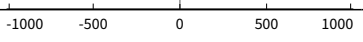
Analysis 1.2. Comparison 1 Fibrin sealant versus control (blood transfusion), Outcome 2 No. exposed to allogeneic blood - type of surgery.

Study or subgroup	FS n/N	Control n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.2.1 Orthopaedic surgery					
Lassen 2006	16/33	21/36		3.35%	-0.1[-0.33,0.14]
Levy 1999	5/29	16/29		3.5%	-0.38[-0.61,-0.15]
Mawatari 2006	0/50	0/50		10.16%	0[-0.04,0.04]
Molloy 2007	7/50	11/50		5.66%	-0.08[-0.23,0.07]
Stutz 2004	0/10	2/11		2.89%	-0.18[-0.44,0.08]
Wang 2001	9/25	14/28		2.83%	-0.14[-0.4,0.12]
Wang 2003	11/38	18/43		3.97%	-0.13[-0.34,0.08]
Subtotal (95% CI)	**235**	**247**		**32.37%**	**-0.14[-0.3,0.03]**
Total events: 48 (FS), 82 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=44.19, df=6(P<0.0001); I^2=86.42%					
Test for overall effect: Z=1.58(P=0.11)					
1.2.2 Prostate surgery					
Gasser 1983	9/44	17/28		3.73%	-0.4[-0.62,-0.19]
Vecsey 1980	0/20	3/20		4.91%	-0.15[-0.32,0.02]
Subtotal (95% CI)	**64**	**48**		**8.64%**	**-0.27[-0.55,0.01]**
Total events: 9 (FS), 20 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=4, df=1(P=0.05); I^2=75.02%					
Test for overall effect: Z=1.91(P=0.06)					
1.2.3 Liver surgery					
Figueras 2007	40/150	29/150		7.9%	0.07[-0.02,0.17]
Noun 1996	7/38	11/44		4.75%	-0.07[-0.24,0.11]
Subtotal (95% CI)	**188**	**194**		**12.65%**	**0.02[-0.11,0.15]**
Total events: 47 (FS), 40 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.83, df=1(P=0.18); I^2=45.46%					
Test for overall effect: Z=0.38(P=0.71)					
1.2.4 Pancreatic surgery					
Lillemoe 2004	0/58	0/66		10.35%	0[-0.03,0.03]
Subtotal (95% CI)	**58**	**66**		**10.35%**	**0[-0.03,0.03]**
Total events: 0 (FS), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.2.5 Thoracic surgery					
Belboul 2004	0/20	0/20		8.02%	0[-0.09,0.09]
Fabian 2003	0/50	0/50		10.16%	0[-0.04,0.04]
Subtotal (95% CI)	**70**	**70**		**18.18%**	**0[-0.04,0.04]**
Total events: 0 (FS), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Not applicable					
1.2.6 Vascular surgery					
Sintler 2005	0/10	3/10		2.31%	-0.3[-0.6,0]
Subtotal (95% CI)	**10**	**10**		**2.31%**	**-0.3[-0.6,0]**
Total events: 0 (FS), 3 (Control)					
Heterogeneity: Not applicable					



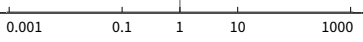
Favours FS Favours Control

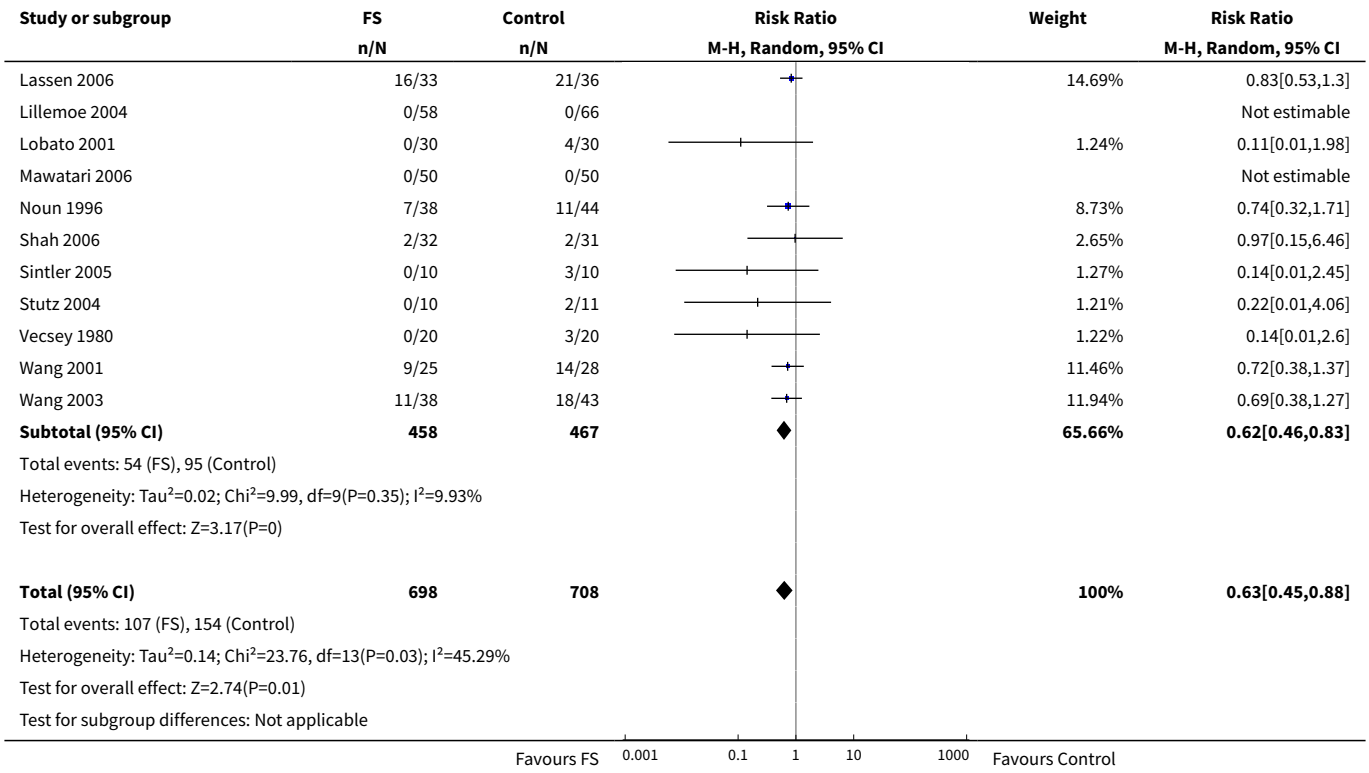
Study or subgroup	FS n/N	Control n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Test for overall effect: Z=1.95(P=0.05)					
1.2.7 Kidney surgery					
Shah 2006	2/32	2/31		6.8%	-0[-0.12,0.12]
Subtotal (95% CI)	**32**	**31**		**6.8%**	**-0[-0.12,0.12]**
Total events: 2 (FS), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.03(P=0.97)					
1.2.8 Cardiac surgery					
Kjaergard 1998	1/11	3/12		2.36%	-0.16[-0.46,0.14]
Subtotal (95% CI)	**11**	**12**		**2.36%**	**-0.16[-0.46,0.14]**
Total events: 1 (FS), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.3)					
1.2.9 Incisional hernia repair					
Lobato 2001	0/30	4/30		6.34%	-0.13[-0.27,-0]
Subtotal (95% CI)	**30**	**30**		**6.34%**	**-0.13[-0.27,-0]**
Total events: 0 (FS), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.98(P=0.05)					
Total (95% CI)	**698**	**708**		**100%**	**-0.07[-0.13,-0.02]**
Total events: 107 (FS), 154 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=74.71, df=17(P<0.0001); I^2=77.25%					
Test for overall effect: Z=2.82(P=0)					
Test for subgroup differences: Not applicable					



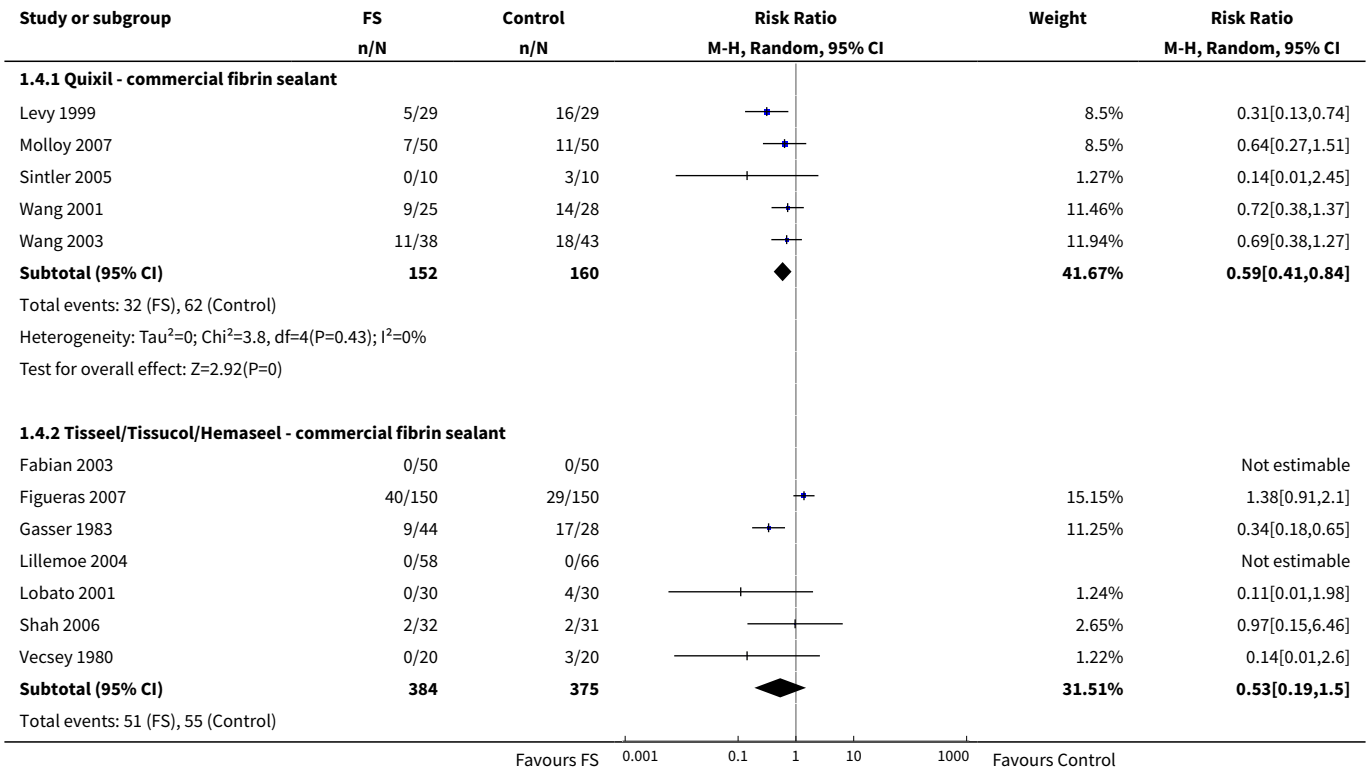
Analysis 1.3. Comparison 1 Fibrin sealant versus control (blood transfusion), Outcome 3 No. exposed to allogeneic blood - transfusion protocol.

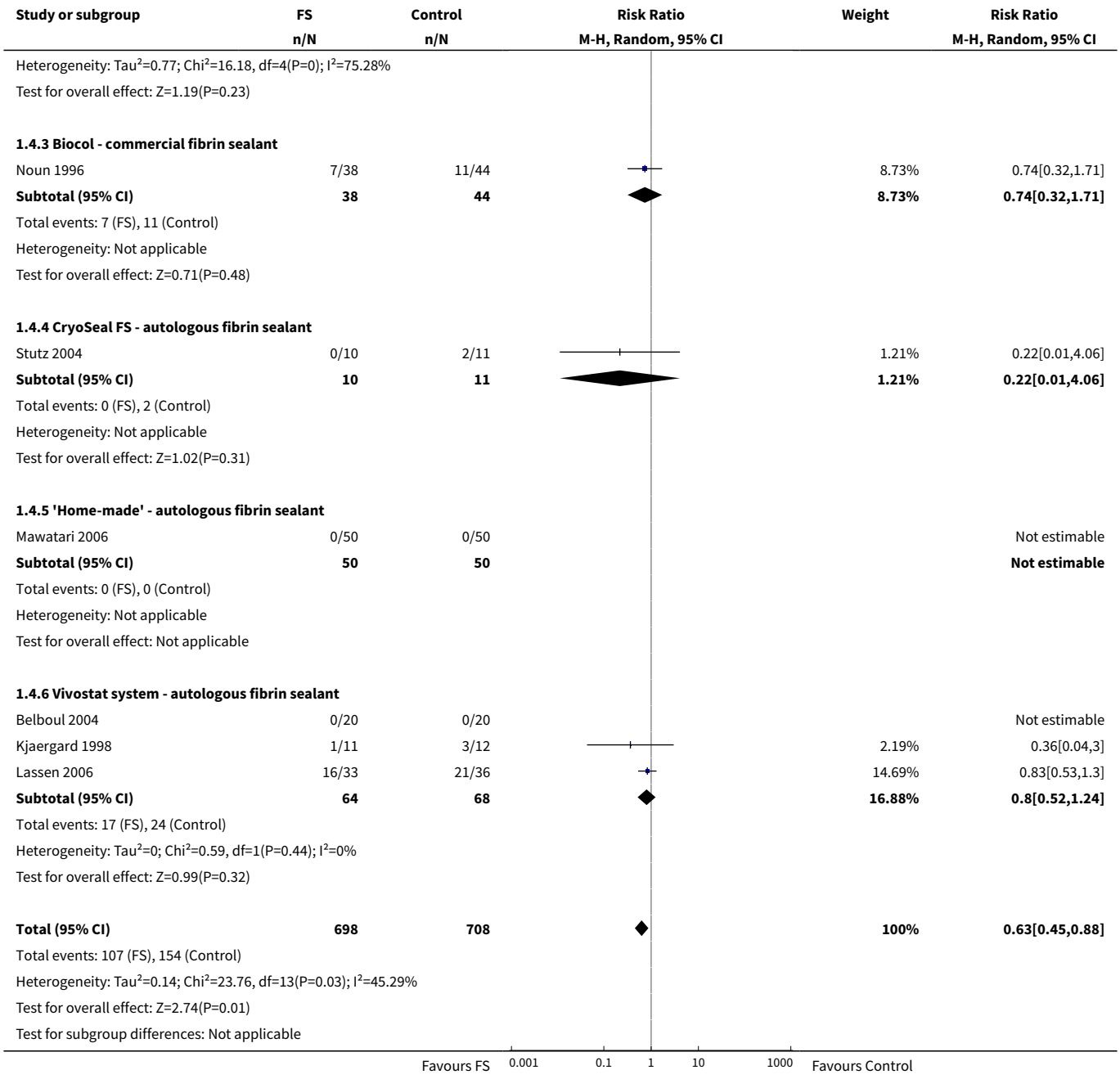
Study or subgroup	FS n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Transfusion protocol					
Figueras 2007	40/150	29/150		15.15%	1.38[0.91,2.1]
Kjaergard 1998	1/11	3/12		2.19%	0.36[0.04,3]
Levy 1999	5/29	16/29		8.5%	0.31[0.13,0.74]
Molloy 2007	7/50	11/50		8.5%	0.64[0.27,1.51]
Subtotal (95% CI)	**240**	**241**		**34.34%**	**0.65[0.28,1.49]**
Total events: 53 (FS), 59 (Control)					
Heterogeneity: Tau^2=0.48; Chi^2=11.06, df=3(P=0.01); I^2=72.87%					
Test for overall effect: Z=1.03(P=0.3)					
1.3.2 No transfusion protocol					
Belboul 2004	0/20	0/20			Not estimable
Fabian 2003	0/50	0/50			Not estimable
Gasser 1983	9/44	17/28		11.25%	0.34[0.18,0.65]



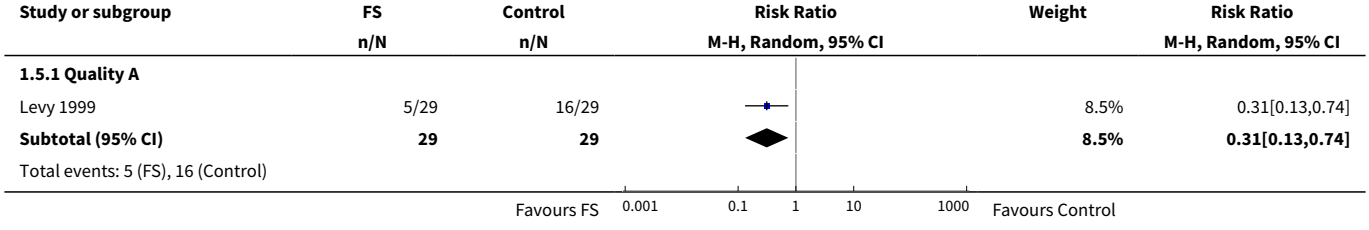


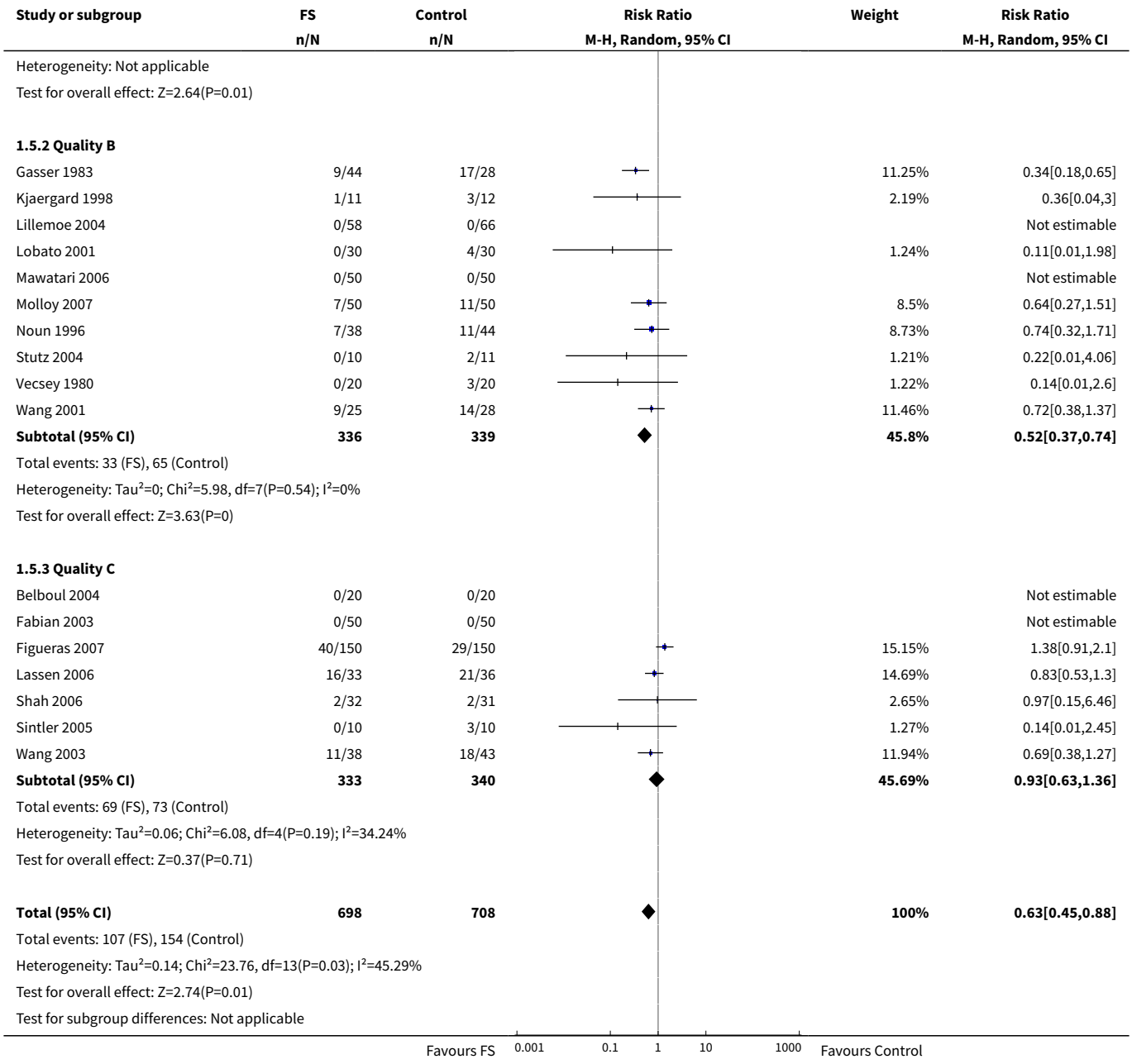
Analysis 1.4. Comparison 1 Fibrin sealant versus control (blood transfusion), Outcome 4 No. exposed to allogeneic blood - type of fibrin sealant.





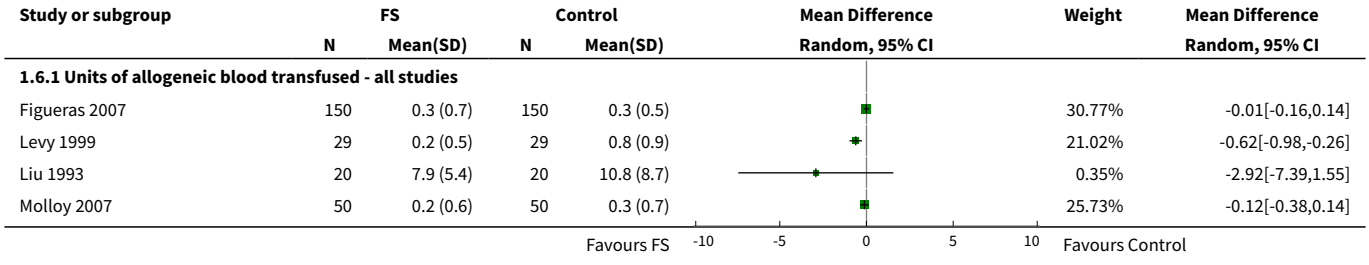
Analysis 1.5. Comparison 1 Fibrin sealant versus control (blood transfusion), Outcome 5 No. exposed to allogeneic blood - methodological quality.



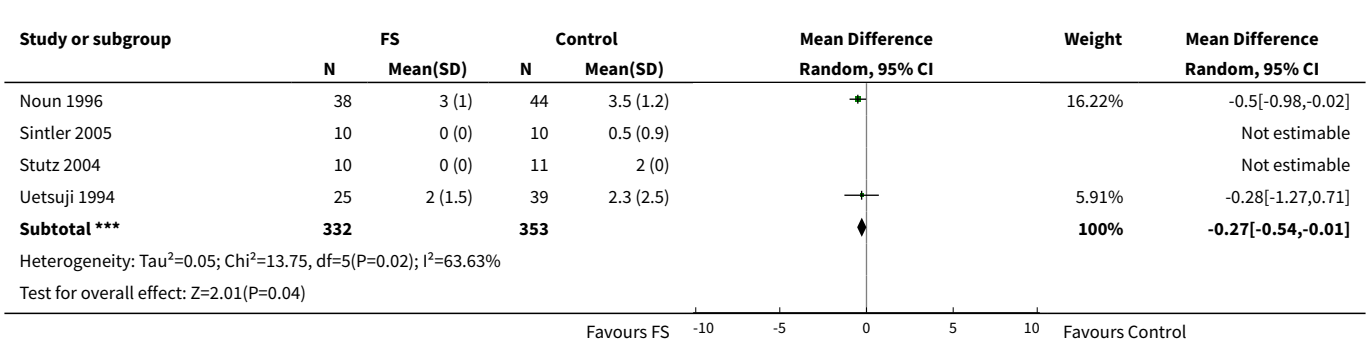


Study or subgroup	FS n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=2.64(P=0.01)					
1.5.2 Quality B					
Gasser 1983	9/44	17/28		11.25%	0.34[0.18,0.65]
Kjaergard 1998	1/11	3/12		2.19%	0.36[0.04,3]
Lillemoe 2004	0/58	0/66			Not estimable
Lobato 2001	0/30	4/30		1.24%	0.11[0.01,1.98]
Mawatari 2006	0/50	0/50			Not estimable
Molloy 2007	7/50	11/50		8.5%	0.64[0.27,1.51]
Noun 1996	7/38	11/44		8.73%	0.74[0.32,1.71]
Stutz 2004	0/10	2/11		1.21%	0.22[0.01,4.06]
Vecsey 1980	0/20	3/20		1.22%	0.14[0.01,2.6]
Wang 2001	9/25	14/28		11.46%	0.72[0.38,1.37]
Subtotal (95% CI)	**336**	**339**		**45.8%**	**0.52[0.37,0.74]**
Total events: 33 (FS), 65 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.98, df=7(P=0.54); I^2=0%					
Test for overall effect: Z=3.63(P=0)					
1.5.3 Quality C					
Belboul 2004	0/20	0/20			Not estimable
Fabian 2003	0/50	0/50			Not estimable
Figueras 2007	40/150	29/150		15.15%	1.38[0.91,2.1]
Lassen 2006	16/33	21/36		14.69%	0.83[0.53,1.3]
Shah 2006	2/32	2/31		2.65%	0.97[0.15,6.46]
Sintler 2005	0/10	3/10		1.27%	0.14[0.01,2.45]
Wang 2003	11/38	18/43		11.94%	0.69[0.38,1.27]
Subtotal (95% CI)	**333**	**340**		**45.69%**	**0.93[0.63,1.36]**
Total events: 69 (FS), 73 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=6.08, df=4(P=0.19); I^2=34.24%					
Test for overall effect: Z=0.37(P=0.71)					
Total (95% CI)	**698**	**708**		**100%**	**0.63[0.45,0.88]**
Total events: 107 (FS), 154 (Control)					
Heterogeneity: Tau^2=0.14; Chi^2=23.76, df=13(P=0.03); I^2=45.29%					
Test for overall effect: Z=2.74(P=0.01)					
Test for subgroup differences: Not applicable					

Analysis 1.6. Comparison 1 Fibrin sealant versus control (blood transfusion), Outcome 6 Units of allogeneic blood transfused - all studies.



Study or subgroup	FS N	FS Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 Units of allogeneic blood transfused - all studies							
Figueras 2007	150	0.3 (0.7)	150	0.3 (0.5)		30.77%	-0.01[-0.16,0.14]
Levy 1999	29	0.2 (0.5)	29	0.8 (0.9)		21.02%	-0.62[-0.98,-0.26]
Liu 1993	20	7.9 (5.4)	20	10.8 (8.7)		0.35%	-2.92[-7.39,1.55]
Molloy 2007	50	0.2 (0.6)	50	0.3 (0.7)		25.73%	-0.12[-0.38,0.14]



Comparison 2. Fibrin sealant versus control (blood loss)

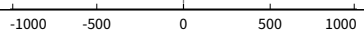
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood loss (total post-operative) - all studies	14	853	Mean Difference (IV, Random, 95% CI)	-161.39 [-224.53, -98.25]
2 Blood loss (total post-operative) - type of surgery	14	853	Mean Difference (IV, Random, 95% CI)	-161.39 [-224.53, -98.25]
2.1 Orthopaedic surgery	7	482	Mean Difference (IV, Random, 95% CI)	-222.52 [-325.18, -119.85]
2.2 Liver surgery	2	139	Mean Difference (IV, Random, 95% CI)	-107.90 [-370.68, 154.88]
2.3 Prostate surgery	3	142	Mean Difference (IV, Random, 95% CI)	-70.25 [-136.59, -3.90]
2.4 Thoracic surgery	2	90	Mean Difference (IV, Random, 95% CI)	-161.99 [-586.20, 262.21]
3 Blood loss (total intra-operative) - all studies	7	463	Mean Difference (IV, Random, 95% CI)	-4.51 [-36.86, 27.83]
4 Blood loss (total intra-operative) - type of surgery	7	463	Mean Difference (IV, Random, 95% CI)	-4.51 [-36.86, 27.83]
4.1 Liver surgery	3	166	Mean Difference (IV, Random, 95% CI)	-124.92 [-545.32, 295.48]
4.2 Vascular surgery	1	47	Mean Difference (IV, Random, 95% CI)	10.70 [-54.98, 76.38]
4.3 Orthopaedic surgery	3	250	Mean Difference (IV, Random, 95% CI)	-8.48 [-45.79, 28.84]
5 Blood loss (total intra- + post-operative) - all studies	4	502	Mean Difference (IV, Random, 95% CI)	-216.18 [-406.26, -26.10]

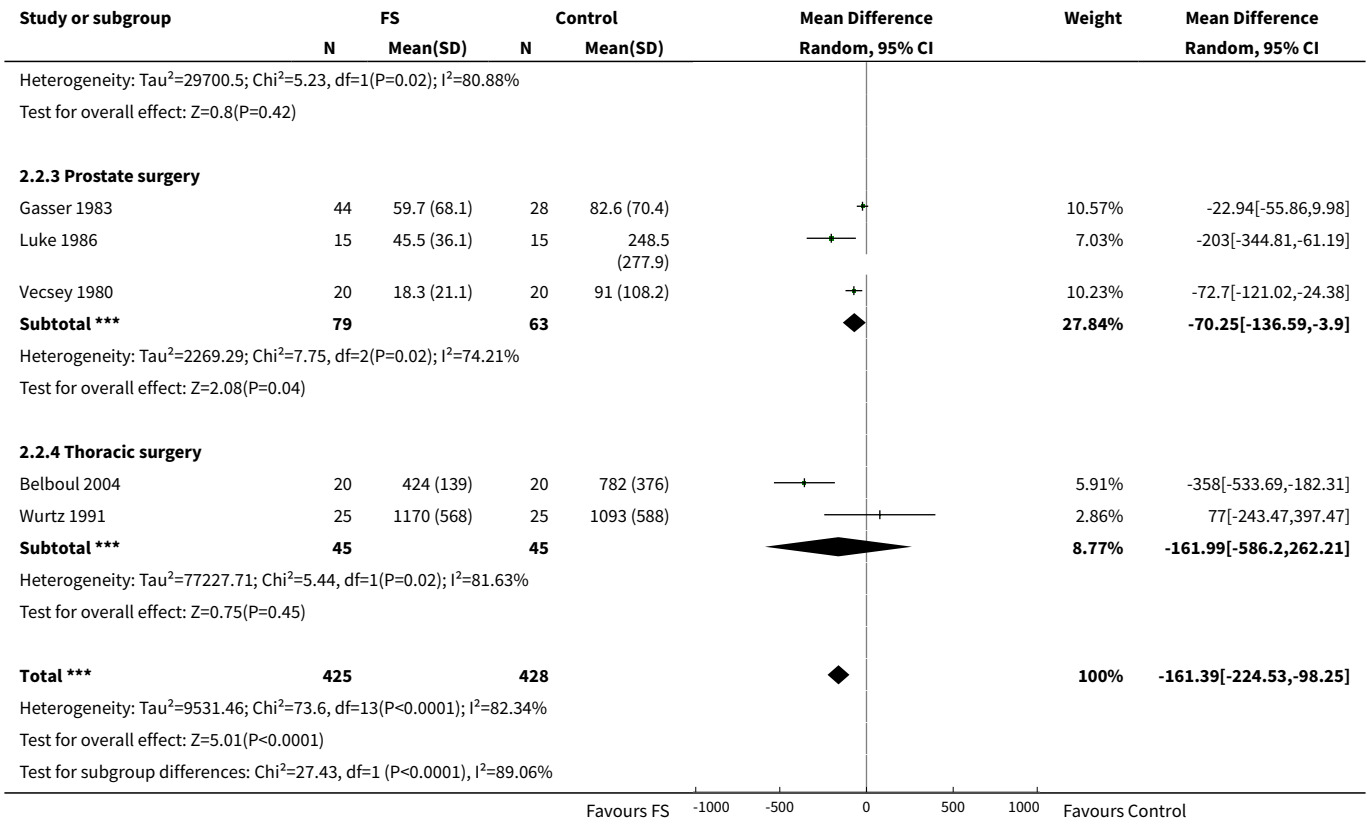
Analysis 2.1. Comparison 2 Fibrin sealant versus control (blood loss), Outcome 1 Blood loss (total post-operative) - all studies.

Study or subgroup	FS N	FS Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Belboul 2004	20	424 (139)	20	782 (376)		5.91%	-358[-533.69,-182.31]
Gasser 1983	44	59.7 (68.1)	28	82.6 (70.4)		10.57%	-22.94[-55.86,9.98]
Kohno 1992	31	164 (147)	31	156 (177)		9.23%	8[-72.99,88.99]
Lassen 2006	33	716 (278.7)	36	791 (288.7)		7.31%	-75[-208.92,58.92]
Levy 1999	29	1063 (482)	29	1768 (614.6)		3.4%	-705[-989.26,-420.74]
Luke 1986	15	45.5 (36.1)	15	248.5 (277.9)		7.03%	-203[-344.81,-61.19]
Mawatari 2006	50	580 (240)	50	810 (341)		7.98%	-230[-345.58,-114.42]
Molloy 2007	50	1190 (490)	50	1415 (416)		5.83%	-225[-403.16,-46.84]
Noun 1996	35	242 (249)	42	505 (666)		4.75%	-263[-480.66,-45.34]
Stutz 2004	10	328.6 (164.3)	11	610 (175.8)		6.9%	-281.4[-426.89,-135.91]
Vecsey 1980	20	18.3 (21.1)	20	91 (108.2)		10.23%	-72.7[-121.02,-24.38]
Wang 2001	25	184.5 (138.6)	28	408.3 (261.9)		8.14%	-223.8[-334.99,-112.61]
Wang 2003	38	163.2 (128.6)	43	244.8 (154.3)		9.86%	-81.6[-143.23,-19.97]
Wurtz 1991	25	1170 (568)	25	1093 (588)		2.86%	77[-243.47,397.47]
Total * **	**425**		**428**			**100%**	**-161.39[-224.53,-98.25]**
Heterogeneity: Tau^2=9531.46; Chi^2=73.6, df=13(P<0.0001); I^2=82.34%							
Test for overall effect: Z=5.01(P<0.0001)							

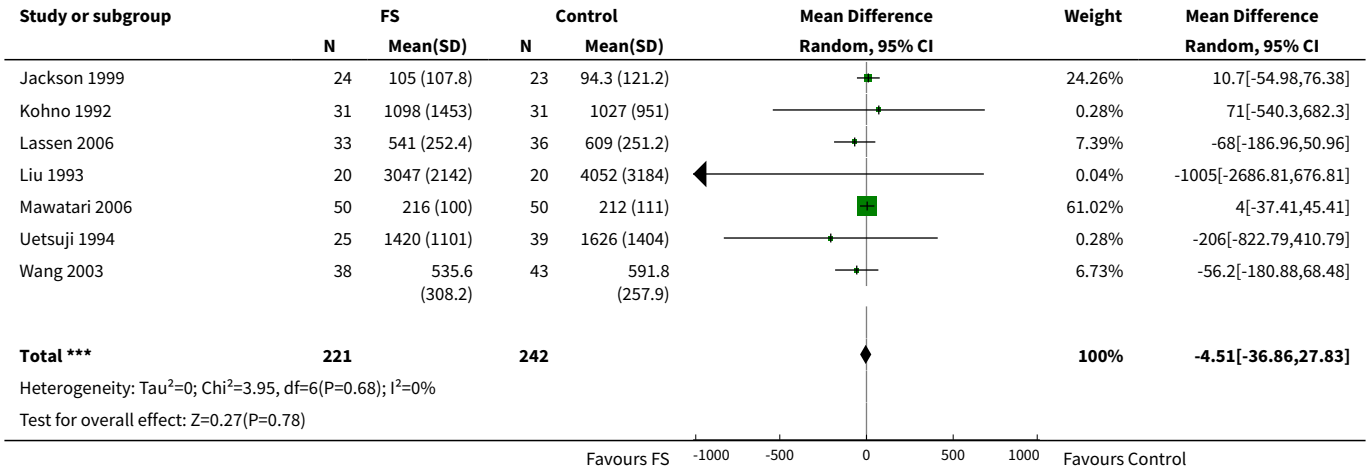
Analysis 2.2. Comparison 2 Fibrin sealant versus control (blood loss), Outcome 2 Blood loss (total post-operative) - type of surgery.

Study or subgroup	FS N	FS Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.2.1 Orthopaedic surgery							
Lassen 2006	33	716 (278.7)	36	791 (288.7)		7.31%	-75[-208.92,58.92]
Levy 1999	29	1063 (482)	29	1768 (614.6)		3.4%	-705[-989.26,-420.74]
Mawatari 2006	50	580 (240)	50	810 (341)		7.98%	-230[-345.58,-114.42]
Molloy 2007	50	1190 (490)	50	1415 (416)		5.83%	-225[-403.16,-46.84]
Stutz 2004	10	328.6 (164.3)	11	610 (175.8)		6.9%	-281.4[-426.89,-135.91]
Wang 2001	25	184.5 (138.6)	28	408.3 (261.9)		8.14%	-223.8[-334.99,-112.61]
Wang 2003	38	163.2 (128.6)	43	244.8 (154.3)		9.86%	-81.6[-143.23,-19.97]
Subtotal * **	**235**		**247**			**49.41%**	**-222.52[-325.18,-119.85]**
Heterogeneity: Tau^2=13788.5; Chi^2=27.74, df=6(P=0); I^2=78.37%							
Test for overall effect: Z=4.25(P<0.0001)							
2.2.2 Liver surgery							
Kohno 1992	31	164 (147)	31	156 (177)		9.23%	8[-72.99,88.99]
Noun 1996	35	242 (249)	42	505 (666)		4.75%	-263[-480.66,-45.34]
Subtotal * **	**66**		**73**			**13.98%**	**-107.9[-370.68,154.88]**



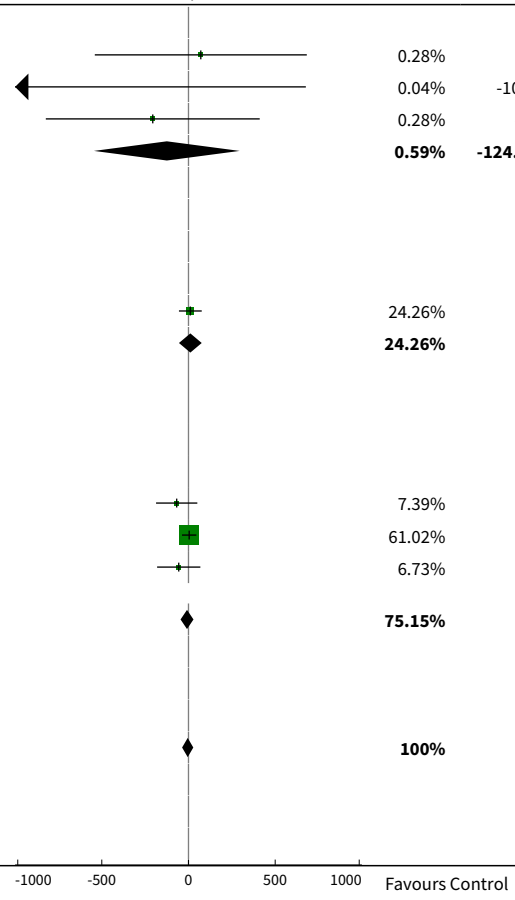


Analysis 2.3. Comparison 2 Fibrin sealant versus control (blood loss), Outcome 3 Blood loss (total intra-operative) - all studies.



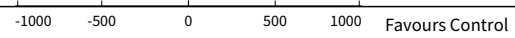
Analysis 2.4. Comparison 2 Fibrin sealant versus control (blood loss), Outcome 4 Blood loss (total intra-operative) - type of surgery.

Study or subgroup	FS N	FS Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.4.1 Liver surgery							
Kohno 1992	31	1098 (1453)	31	1027 (951)		0.28%	71[-540.3,682.3]
Liu 1993	20	3047 (2142)	20	4052 (3184)		0.04%	-1005[-2686.81,676.81]
Uetsuji 1994	25	1420 (1101)	39	1626 (1404)		0.28%	-206[-822.79,410.79]
Subtotal ***	**76**		**90**			**0.59%**	**-124.92[-545.32,295.48]**
Heterogeneity: Tau^2=0; Chi^2=1.51, df=2(P=0.47); I^2=0%							
Test for overall effect: Z=0.58(P=0.56)							
2.4.2 Vascular surgery							
Jackson 1999	24	105 (107.8)	23	94.3 (121.2)		24.26%	10.7[-54.98,76.38]
Subtotal ***	**24**		**23**			**24.26%**	**10.7[-54.98,76.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.32(P=0.75)							
2.4.3 Orthopaedic surgery							
Lassen 2006	33	541 (252.4)	36	609 (251.2)		7.39%	-68[-186.96,50.96]
Mawatari 2006	50	216 (100)	50	212 (111)		61.02%	4[-37.41,45.41]
Wang 2003	38	535.6 (308.2)	43	591.8 (257.9)		6.73%	-56.2[-180.88,68.48]
Subtotal ***	**121**		**129**			**75.15%**	**-8.48[-45.79,28.84]**
Heterogeneity: Tau^2=0; Chi^2=1.87, df=2(P=0.39); I^2=0%							
Test for overall effect: Z=0.45(P=0.66)							
Total ***	**221**		**242**			**100%**	**-4.51[-36.86,27.83]**
Heterogeneity: Tau^2=0; Chi^2=3.95, df=6(P=0.68); I^2=0%							
Test for overall effect: Z=0.27(P=0.78)							
Test for subgroup differences: Chi^2=0.56, df=1 (P=0.75), I^2=0%							



Analysis 2.5. Comparison 2 Fibrin sealant versus control (blood loss), Outcome 5 Blood loss (total intra- + post-operative) - all studies.

Study or subgroup	FS N	FS Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Figueras 2007	150	1180 (2528)	150	960 (1253)		12.04%	220[-231.52,671.52]
Mawatari 2006	50	788 (268)	50	1017 (364)		32.27%	-229[-354.29,-103.71]
Stutz 2004	10	526 (317.1)	11	1033 (170.1)		24.92%	-507[-727.75,-286.25]
Wang 2003	38	698.7 (338)	43	836.6 (327.2)		30.78%	-137.9[-283.2,7.4]
Total ***	**248**		**254**			**100%**	**-216.18[-406.26,-26.1]**
Heterogeneity: Tau^2=25062.68; Chi^2=11.38, df=3(P=0.01); I^2=73.64%							
Test for overall effect: Z=2.23(P=0.03)							

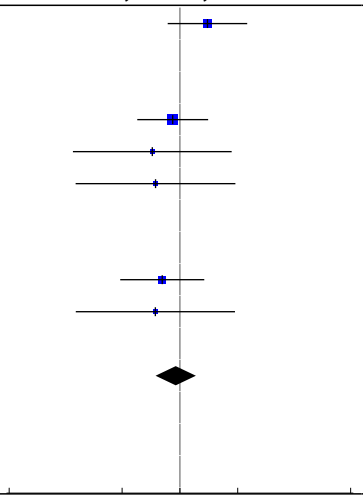


Comparison 3. Adverse events and other outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	10	1014	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.38, 1.89]
2 Re-operation for bleeding	3	340	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.18, 21.82]
3 Infection - any infection	9	914	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.44, 1.94]
4 Infection - wound infection	6	504	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.24, 1.58]
5 Haematoma	4	482	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.18, 1.18]
6 Stroke	3	84	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.02, 7.99]
7 Deep vein thrombosis	2	400	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 71.92]
8 Pulmonary embolus	3	420	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.11, 8.88]
9 Length of hospital stay	5	614	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.42, 0.01]

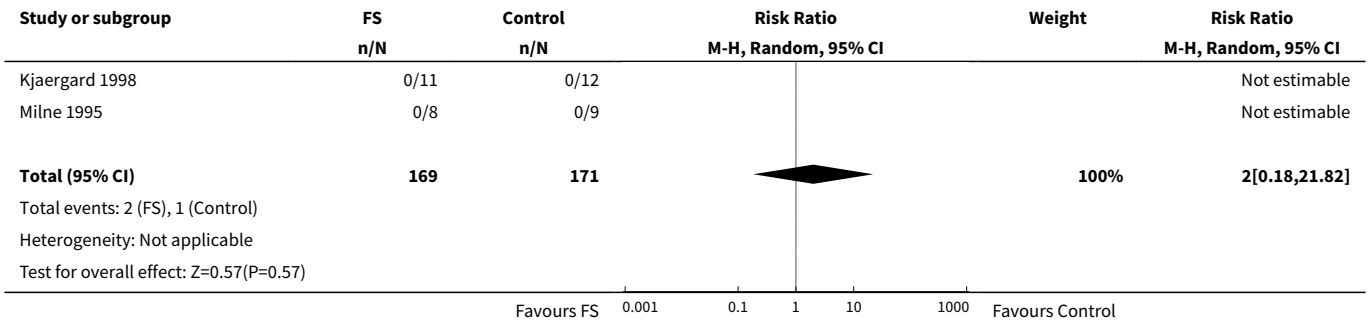
Analysis 3.1. Comparison 3 Adverse events and other outcomes, Outcome 1 Mortality.

Study or subgroup	FS n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Figueras 2007	6/150	2/150		25.62%	3[0.62,14.63]
Jackson 1999	0/24	0/23			Not estimable
Kjaergard 1998	0/11	0/12			Not estimable
Kohno 1992	3/31	4/31		32.26%	0.75[0.18,3.08]
Levy 1999	0/29	1/29		6.44%	0.33[0.01,7.86]
Lillemoe 2004	0/58	1/66		6.35%	0.38[0.02,9.12]
Molloy 2007	0/50	0/50			Not estimable
Sintler 2005	0/10	0/10			Not estimable
Taylor 2003	2/100	4/99		22.93%	0.5[0.09,2.64]
Wang 2003	0/38	1/43		6.39%	0.38[0.02,8.97]
Total (95% CI)	**501**	**513**		**100%**	**0.85[0.38,1.89]**
Total events: 11 (FS), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.71, df=5(P=0.59); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					

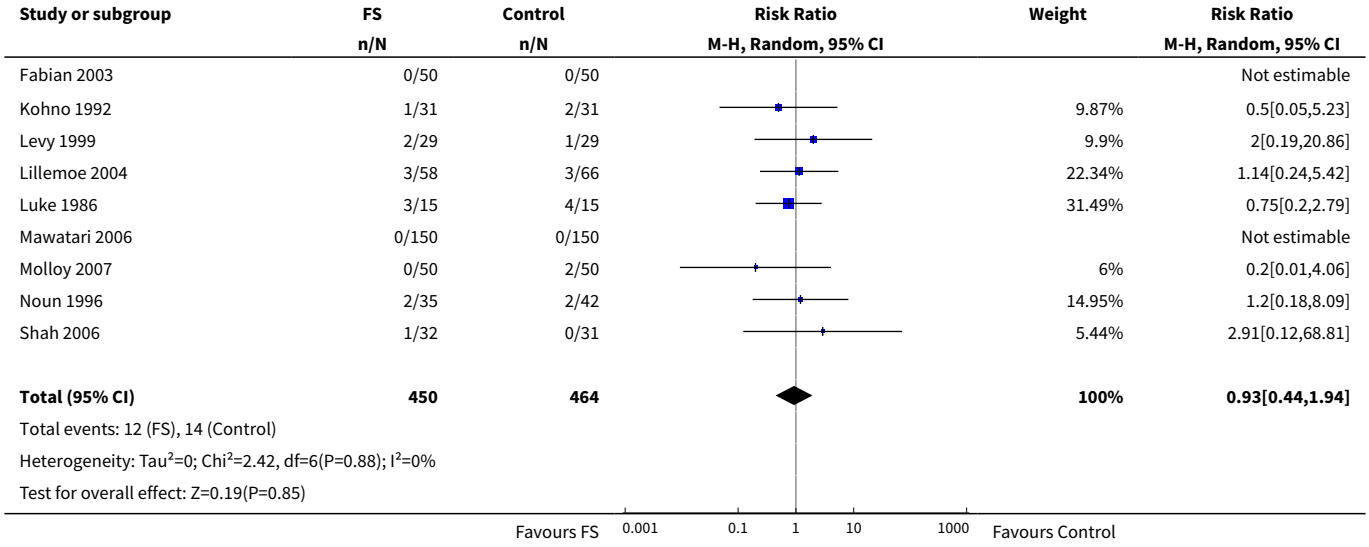


Analysis 3.2. Comparison 3 Adverse events and other outcomes, Outcome 2 Re-operation for bleeding.

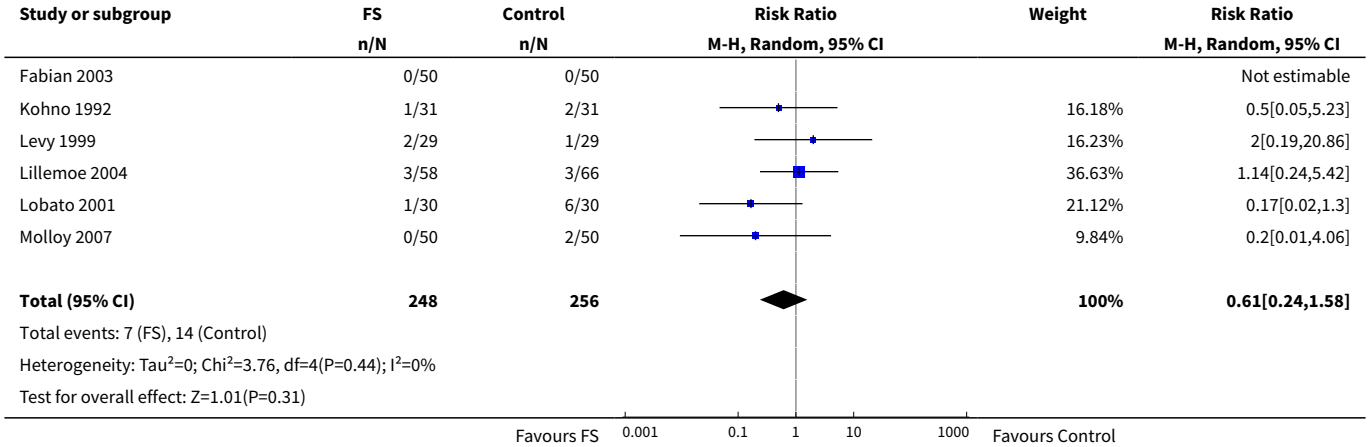
Study or subgroup	FS n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Figueras 2007	2/150	1/150		100%	2[0.18,21.82]



Analysis 3.3. Comparison 3 Adverse events and other outcomes, Outcome 3 Infection - any infection.

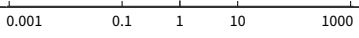


Analysis 3.4. Comparison 3 Adverse events and other outcomes, Outcome 4 Infection - wound infection.



Analysis 3.5. Comparison 3 Adverse events and other outcomes, Outcome 5 Haematoma.

Study or subgroup	FS n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Figueras 2007	1/150	0/150		8.68%	3[0.12,73.06]
Lassen 2006	2/33	4/36		33.3%	0.55[0.11,2.78]
Lobato 2001	2/30	6/30		38.4%	0.33[0.07,1.52]
Wang 2001	1/25	4/28		19.62%	0.28[0.03,2.34]
Total (95% CI)	**238**	**244**		**100%**	**0.46[0.18,1.18]**
Total events: 6 (FS), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.75, df=3(P=0.63); I^2=0%					
Test for overall effect: Z=1.62(P=0.11)					



Analysis 3.6. Comparison 3 Adverse events and other outcomes, Outcome 6 Stroke.

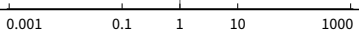
Study or subgroup	FS n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Jackson 1999	0/24	0/23			Not estimable
Milne 1995	0/8	1/9		100%	0.37[0.02,7.99]
Sintler 2005	0/10	0/10			Not estimable
Total (95% CI)	**42**	**42**		**100%**	**0.37[0.02,7.99]**
Total events: 0 (FS), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					

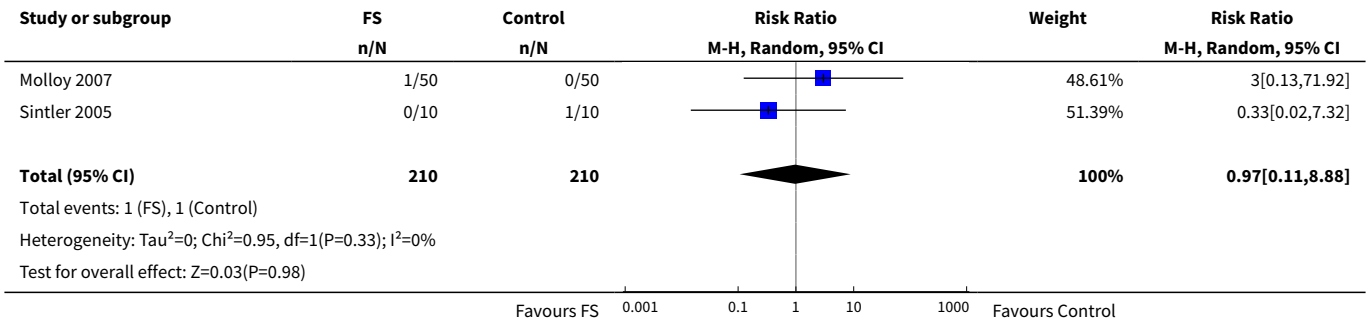
Analysis 3.7. Comparison 3 Adverse events and other outcomes, Outcome 7 Deep vein thrombosis.

Study or subgroup	FS n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mawatari 2006	0/150	0/150			Not estimable
Molloy 2007	1/50	0/50		100%	3[0.13,71.92]
Total (95% CI)	**200**	**200**		**100%**	**3[0.13,71.92]**
Total events: 1 (FS), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					

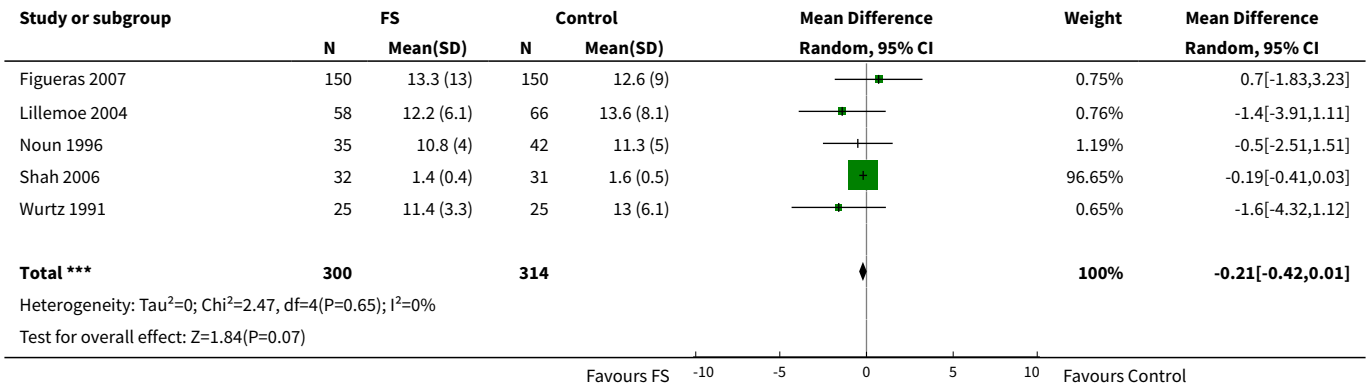
Analysis 3.8. Comparison 3 Adverse events and other outcomes, Outcome 8 Pulmonary embolus.

Study or subgroup	FS n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mawatari 2006	0/150	0/150			Not estimable





Analysis 3.9. Comparison 3 Adverse events and other outcomes, Outcome 9 Length of hospital stay.



APPENDICES

Appendix 1. Detailed search strategies

The Cochrane Central Register of Controlled Trials (CENTRAL) and the databases MEDLINE and EMBASE were initially searched using unrestricted search terms with exploded MeSH (medical subject heading) terms and specific text-word terms for fibrin sealant.

- The exploded MeSH terms included: 'fibrin tissue adhesive' and 'fibrin glue'.
- The specific text-word terms included: fibrin glue$, fibrin sealant$, fibrin seal$, biological glue$ or biological seal$, beriplast, bolheal, tissucol, tisseel, quixil, biocol, cryoseal.
- To maximise the sensitivity for the retrieval of all potentially relevant studies, electronic searches of MEDLINE and EMBASE were initially unrestricted. To improve the specificity of the updated electronic searches two search filters were used.
- Firstly, the ISPOT filter (Laupacis 1997) which identifies blood transfusion trials.
- Secondly, an RCT filter (Dickersin 1994; Robinson 2002), which primarily identifies randomised controlled trials.
- These search filters were coupled with the MeSH headings and the text-word terms for fibrin sealant.

NB: The truncation character "$" (dollar sign) indicates the use of unlimited truncation to retrieve all possible suffix variations of the root word or phrase.

MEDLINE
Search dates: 1950 to 1 March 2008
1 exp Fibrin tissue adhesive/
2 fibrin glu$.tw.
3 fibrin sealant$.tw.
4 fibrin seal$.tw.
5 biological glu$.tw.

6 biological seal$.tw.
7 Beriplast.tw.
8 Bolheal.tw.
9 Collaseal.tw.
10 Tissucol.tw.
11 Tisseel.tw.
12 Quixil.tw.
13 Biocol.tw.
14 Omrixil.tw.
15 Vivostat.tw.
16 Hemaseel.tw.
17 Crosseal.tw.
18 or/1-17
19 exp Blood Transfusion/
20 exp Hemorrhage/
21 exp Anesthesia/
22 transfusion$.tw
23 bleed$.tw
24 blood loss$.tw
25 hemorrhag$.tw
26 or/19-25
27 randomized controlled trial.pt
28 controlled clinical trial.pt
29 randomized controlled trials.sh
30 random allocation.sh
31 double blind method.sh
32 single blind method.sh
33 or/27-32
34 clinical trial.pt
35 exp Clinical trials/
36 (clin$ adj25 trial$).ti,ab
37 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
38 placebos.sh
39 placebo$.ti,ab
40 random$.ti,ab
41 research design.sh
42 or/34-41
43 comparative study.sh
44 exp Evaluation studies/
45 follow up studies.sh
46 prospective studies.sh
47 (control$ or prospectiv$ or volunteer$).ti,ab
48 or/43-47
49 33 or 42 or 48
50 18 and 26 and 49
51 limit 50 to human

EMBASE
Search dates: 1980 to March 2008
1 exp Fibrin glue/
2 fibrin glue$.tw
3 fibrin sealant$.tw
4 fibrin seal$.tw
5 (biological glue$ or biological seal$).tw
6 (beriplast or bolheal or collaseal or tissucol or tisseel or tachocomb or quixil or biocol). tw
7 or/1-6
8 exp Blood transfusion/
9 exp Bleeding/
10 exp Anesthesia/
11 transfusion$.tw
12 bleed$.tw
13 blood loss$.tw

14 hemorrhag$.tw
15 or/8-14
16 7 and 15
17 exp clinical trial/
18 controlled study/
19 randomized controlled trial$.tw
20 comparative stud$.ti,ab
21 random allocation.tw
22 crossover trial.ti,ab
23 double blind procedure.sh
24 (cli$ adj25 trial$).ti,ab
25 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab
26 placebo$.sh
27 placebo$.ti,ab. or placebo$.tw
28 random$.ti,ab. or random$.tw
29 or/17-28
30 animal/ not (human/ and animal/)
31 29 not 30
32 "COMPARATIVE STUDY".mp
33 "EVALUATION STUDIES".mp
34 "FOLLOW UP STUDIES".mp
35 "CROSSOVER TRIAL$".mp
36 exp prospective study/
37 exp longitudinal study/
38 (control$ or prospectiv$ or volunteer$).ti,ab
39 or/32-38
40 39 not 30
41 31 or 40
42 16 and 41
43 limit 42 to human

CENTRAL (Issue 3, 2007)
#1 Fibrin Tissue Adhesive/
#2 (fibrin and glue*)
#3 (fibrin and seal*)
#4 (fibrin and sealant*)
#5 ((biological and glue*) or (biological and seal*))
#6 (beriplast or bolheal or collaseal or tissucol or tisseel or quixil or biocol or omrixil or vivostat or hemaseel or crosseal)
#7 #1 or #2 or #3 or #4 or #5 or #6

WHAT'S NEW

Date	Event	Description
1 May 2009	Amended	The risk of bias table is expanded, and risk of bias figures are included.

HISTORY

Review first published: Issue 2, 2003

Date	Event	Description
12 March 2008	New search has been performed	Updated review.

Date	Event	Description
		The searches were updated in March 2008. An additional 12 trials were included in the review. The text of the review was updated to reflect changes to the results.

CONTRIBUTIONS OF AUTHORS

Danielle Anthony (University of Newcastle): quality assessed the trials.

Paul Carless (University of Newcastle): developed search strategies, performed searches, obtained relevant papers, applied inclusion and exclusion criteria to retrieved papers, quality assessed trials, extracted and entered trial data into Review Manager, entered all study details into Review Manager, co-ordinated the project, and wrote the review.

David Henry (University of Newcastle): provided methodological expertise.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Health and Medical Research Council of Australia, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

*Erythrocyte Transfusion; Blood Loss, Surgical [*prevention & control]; Blood Transfusion; Elective Surgical Procedures; Fibrin Tissue Adhesive [*therapeutic use]; Hemostatics [*therapeutic use]; Randomized Controlled Trials as Topic; Transplantation, Homologous

MeSH check words

Adult; Humans